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PANEL DISCUSSION ON PROBLEMS IN THE DIAGNOSIS AND MANAGEMENT OF CARDIOVASCULAR DISEASE*

Moderator: SIMON DACK, M.D., Assistant Clinical Professor of Medicine, New York Medical College, and Associate Attending in Cardiology, Mount Sinai Hospital, New York, N. Y.

Panelists: MILTON LANDOWNE, M.D., formerly Assistant Chief, Section on Gerontology, National Heart Institute, NIH, USPHS, Bethesda; Baltimore City Hospital, Baltimore; at present, Medical Director, Levindale Hebrew Home and Infirmary, and Head, Chronic Disease Division, Sinai Hospital, Baltimore, Md.
"Present Status and Newer Trends in Cardiovascular Research in the Aged."

ALDO A. LUISADA, M.D., Associate Professor of Medicine and Director, Division of Cardiology, Chicago Medical School, Chicago, Illinois.
"Cardiac Diagnostic Methods in the Old Age Group."

JOHN H. BLAND, M.D., Associate Professor of Medicine, University of Vermont College of Medicine, and Attending Physician, Mary Fletcher and Degoesbriand Memorial Hospitals, Burlington, Vermont.
"Problems of Edema and Electrolyte Disturbances in the Aged."

RAYMOND HARRIS, M.D., Assistant Medical Director, Ann Lee Home, and Chief of Cardiology, St. Peter's Hospital, Albany, N. Y.
"Treatment of Cardiovascular Disorders in the Aged."

MODERATOR SIMON DACK: Our subject is a broad one. As the basis for discussion, I have asked each member of the panel to prepare a short preliminary talk concerning a phase of this problem in which he has been specifically interested.

A most interesting part of this discussion will be the questions and answers after each panelist has spoken. The success of the panel will depend upon how well the panel members are stimulated with questions.

Dr. Milton Landowne will begin with a summary of the "*Present Status and Newer Trends in Cardiovascular Research in the Aged*".

CARDIOVASCULAR RESEARCH

DR. MILTON LANDOWNE: Our moderator has given me a formidable task, which I shall approach by restricting myself to illustration and example.

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Formal research in aging is increasing rapidly, and the number of studies in cardiovascular disease is increasing in proportion. The Center for Aging Research currently notes that the intramural research programs of the National Institutes of Health at Bethesda, Maryland, include some 95 projects which may be designated as related to the field of gerontology. Twelve of these are in the area of cardiovascular research.

The grant-in-aid program of the United States Public Health Service, as of September 1956, included in research conducted by non-government laboratories under Public Health Service grants, about 100 studies related to aging. Seventeen of these could be classified in the cardiovascular field. The American Heart Association's recently announced research awards for 1957 to 155 investigators include 15 projects which, at least by title, are in areas directly related to aging.

I shall not attempt to give a comprehensive or quantitative account of the volume of research in this field. There are many sources of importance in addition to those that I have elected to mention. These are simply examples.

Sound beginnings have been made in the fundamental studies of aging in muscle, connective tissue, cellular metabolism and intercellular transportation which are essential to our understanding of order and disorder in the circulatory system. Papers contributed to gerontological meetings last year in this country, Mexico, England, Holland and Switzerland indicated a growing emphasis on basic matters. It is much too soon to expect these inquiries to yield information of immediate practical value.

It is well to bear in mind that work which would not be classified under the heading of gerontological or geriatric research while in progress, may contribute more to the longevity and well-being of our senior citizens than studies strongly oriented toward aging. Illustrative examples are sanitation, antibiotics and social security. Thus, one cannot complete the chart of cardiovascular research in aging today.

In the important area of arteriosclerosis, a brief survey affords an example of results that may be pertinent and practical in contemporary aging.

There is no need to remind you, if you will forgive an inverted metaphor, of the mesalliance between arteriosclerosis and aging. This follows an intolerable and long-standing custom of common-law marriage—the frail woman (aging) succumbs prematurely, and her heartless husband (arteriosclerosis) survives to confront the statistician. Only the eventual subjugation of arteriosclerosis will change this survivorship pattern, and liberate merry-widowed aging to seek another husband of uncertain fate.

Not all arterioscleroses should be maligned, particularly calcific medial sclerosis, which, although it is clinically and radiographically ostentatious, is largely nondisabling. The true culprit is atherosclerosis, a disorder which has early manifestations in the linings of vessels and becomes localized with devastating efficiency in the coronary arteries.

Current research in arteriosclerosis can be classified with 3 "e's." The first "e" is *essential* studies in arterial tissues and their metabolism. The second is *experimental* counterparts of human disease. The third is *epidemiologic* investi-

gations into the diseases of man. The recently published work of the American Foundation entitled "Medical Research: A Mid-Century Survey" (which I commend highly) summarizes thus: "Current research on arteriosclerosis includes studies of long-neglected problems of structure, function, and metabolism of arterial tissues. Progressively more discernible is the trend toward accumulation of accurate chemical and physical data which will facilitate formulation of arteriosclerosis problems in terms of metabolism . . . clearly, elucidation of the assumed role of cholesterol in arterial disease processes depends upon the prior solution of basic problems in intermediary lipid metabolism generally . . . Lipids . . . formerly considered inert, as depot fat, or metabolically inactive, as cholesterol, are intimately involved in the continuous exchange of metabolic cycles." At the 1955 Geneva Conference on Peaceful Uses of Atomic Energy, Dr. Baird Hastings noted that the use of isotopes in studies of disease involving disorders of lipid metabolism is probably only now about to flower, particularly in relation to arteriosclerosis, obesity, and abnormalities of steroid hormone metabolism.

The experimental counterparts of clinical studies of arteriosclerosis are in full swing. Newly relevant factors appear and are given adequate press coverage daily. I cannot deal with them here, except to urge abstention from fads, especially in geriatric practice where alteration of lifetime patterns is always to be judiciously approached.

In the epidemiologic area, besides the important studies initiated by Dr. Keys on diet, cholesterol and mortality, recent preliminary reports on population groups are of interest. I refer, for example, to the report of the Framingham study after four years, and of the Los Angeles study after nearly three and a half years of operation.

Initially, the Framingham group examined 4,500 people between the ages of 30 and 60 years, taken from the general population. The Los Angeles group examined about half this number of people (city civil service employees) between the ages of 18 and 70 years. In these studies, the prevalence of clinically diagnosed significant coronary artery disease in the older male population was not obscured by the bias of hospital or physicians' office data. These groups represented samplings from the general population or from a sample of the general population. Asymptomatic disease, that is, electrocardiographic evidence of infarction unsupported by clinical angina or infarction, became a recognizable entity in the older age group. The incidence of detectable new disease also increased with age, but not to the same extent as the prevalence three or four years previously. The suggestion that severity and incidence do not keep pace is suggested by the mortality rate in the Los Angeles study. This showed that there was a substantial decrease in the fatality rate according to age among males who had coronary artery disease. In the 40–54 year age group, a man called "normal" had little chance of dying of coronary artery disease, and far less than a man who had coronary artery disease. However, in the older age bracket, twice as many "normal" men (in total count) died of coronary artery disease as did those previously known to have coronary artery disease. This is due to the fact that in the older age group the fatality rate in "normal" subjects

becomes appreciable, and the discrepancy in rate between "normal" men and those with coronary artery disease becomes considerably less.

The increasing frequency of identification (in older subjects especially) of asymptomatic myocardial infarction with the appreciable mortality of ostensibly normal persons from coronary artery disease emphasizes 2 simple facts: 1) at present we are not able to identify persons with coronary artery disease, but we apply this diagnosis to persons with the complications and consequences of coronary artery disease, such as infarction and angina; and 2) the underlying disorder, atherosclerosis of the coronary arteries, is so widespread that its presence cannot be excluded. Atherosclerosis develops over long periods of time and presents a complete spectrum of response on the part of the person, from asymptomatic tolerance and longevity with extensive disease to early and sudden death following early and severe complications. In 1933 Willius *et al.* noted the early and progressive incidence of coronary arteriosclerosis, on the basis of mortality data from the Mayo clinic. Their study showed that gross, morphologic involvement of the coronary arteries by atherosclerosis rose in association with aging—as did the clinical incidence of coronary artery disease in the recent clinical studies just mentioned. Slight and moderate anatomic involvement began in the second decade, and was virtually complete in the 50-year-old group.

Other studies include the outstanding work of Wright, Edwards and Dry. Recently, Holman strikingly delineated the early course of aortic atherosclerosis. His studies of 1,000 necropsy specimens showed that: 1) in the aorta of every person over 3 years of age there are fatty streaks, and 2) fibrous plaques follow fatty streaks by approximately twenty years, on the average.

In view of the general prevalence of atherosclerosis in this country, it is reassuring to know that it does develop slowly, and often permits the development of adaptive collateral function. Coronary artery disease, thus, can be benign and asymptomatic. Therefore it is injudicious, to say the least, to let the classic picture of the complications dominate our handling of older people.

MODERATOR DACK: Thank you, Dr. Landowne. The second member of the panel is Dr. Aldo Luisada who will review the subject of "*Cardiac Diagnostic Methods in the Old Age Group.*"

DIAGNOSTIC METHODS

DR. ALDO A. LUISADA: My knowledge about old people is that of the average physician who sees young, middle-aged, and old people. So far, I have not looked at old people as a separate group. Only recently has this problem come to the fore and our Department started a systematic study in collaboration with Dr. Harris, whom you will hear later. I am going to present a few of the conclusions reached in this study, with the proviso that they are tentative. The data are still being analyzed and the statistics may cause some alterations in these conclusions.

Diagnostic methods for elderly persons are virtually no different from those used for middle-aged and younger people. The only point is that we do not know the range of normalcy in older people. That is why we started a study to determine normal data in people without apparent disease, admitted to an Old Age Home. First there was a general review of the data and of the clinical signs and symptoms for the group as a whole. Then, in order to find what was normal for the aged, the subjects with obvious disease were excluded.

Initially, 500 persons between the ages of 50 and 110 years were examined. *Heart murmurs* were found in only 42 per cent. Most of the murmurs were systolic—at the apex in 22 per cent and at the base in 19 per cent. In rare instances the murmur was diastolic.

Obvious *valvular lesions* can be found in old people. One elderly person had mitral stenosis at the age of 68 years. One had aortic insufficiency at the age of 72. Incidentally, one old man presented complete inversion of his viscera, a fact which did not cause him the least bit of trouble.

What is the *blood pressure* level in older people? In the second phase of our study, blood pressure was determined in 360 elderly persons; in about 78 per cent it was normal. The old rule that the blood pressure should increase with age, is frequently true on an individual basis because older persons have more reasons for higher blood pressure—for example, renal or arterial pathologic conditions. However, this rule does not imply that the elevation is due to "aging." *The aging man or woman frequently has a normal, or even a subnormal, blood pressure.*

Hypertension was found only in 22 per cent of all the subjects. This is significant. The standard for normal blood pressure was considered to be the average normal level for all ages. On this basis, 80 per cent of the subjects had a blood pressure not exceeding 120/80. No instance of high blood pressure was found in persons above the age of 90; thus, in the 90–110 year age group, our subjects had normal blood pressure.

A correlation was found between the blood pressure and various positions of the body. These elderly people were subjected to postural tests in order to see whether the reactivity of the carotid sinus and aortic receptors was modified. In general, following the change from the supine to the standing position, there was a greater drop in blood pressure for those who had a normal blood pressure than for those who had a high blood pressure. Those who had a normal blood pressure had a normal drop, consistent with that found in younger people. This confirms the observation that in people with high blood pressure there may be either a primary or secondary change in the reactivity of the carotid sinus.

The *blood* was studied in 100 persons. In 40 per cent the red blood cell count was 5,000,000 per cu. mm. or more; in 60 per cent the count was slightly lower.

The *size of the heart* is an important clue to the condition of the cardiovascular system. It can be estimated fairly accurately by roentgenography. The heart was studied in 391 persons and found to be of normal size in 43 per cent, slightly enlarged in 40 per cent, moderately enlarged in 13 per cent, and greatly enlarged in only 3.6 per cent.

Among those with hearts of normal size, 18 per cent had a murmur, indicating that the murmur was frequently irrelevant and had no clinical significance.

A *dilated and tortuous aorta* was found only in 23 per cent of the subjects. This should teach roentgenologists to be more cautious when they speak of "senile aorta." I have received x-ray reports of "senile aorta" in people of 20 or even 18 years of age. Even in older people, the fact that the aorta is tortuous should not be attributed to age but to other factors, often to a lesion of the aorta (atherosclerosis).

Carotid tracings were made in order to find out whether or not there was any typical abnormality of the graph. In most of the subjects, the rise of the pulse was slightly more rapid, the fall was slightly slower, and the dicrotic wave was higher, than in younger people, due probably to some degree of rigidity of the aortic wall.

The phonocardiogram was used in a special study to determine the *duration of heart sounds* in the aged. All people with murmurs were excluded, as obviously a murmur would confuse the graph and not permit an accurate measurement. In 100 old people, the average duration of the first heart sound was found to be slightly prolonged but this prolongation was due mostly to vibrations of a vascular type which may occur at the end of the first sound, in the first part of systole. When measurement was limited to the mid-portion of the first sound, namely that due to valvular events, this phase tended to become shorter with increasing age. There also was a tendency towards a decrease in duration of the second sound. Thus, by clinical auscultation one would expect, in older people, to hear snapping and shorter heart sounds. The average duration of mechanical systole, as measured by the interval between the first and second sounds, was 0.33 second. This value must be correlated with the rate, but in general it was similar to the duration in younger people and without any special difference.

The average *pulse rate* was 81 per minute—slightly faster than in younger persons.

The *electrocardiogram* revealed a few abnormalities. Evidence of old infarcts appeared in slightly more than 6 per cent of the persons studied. Complete bundle branch block was found on the left in 2.5 per cent, and on the right in 5.4 per cent; as the percentages were small, no significance could be attached to this difference. Complete auriculo-ventricular block was found in only 0.6 per cent. Ventricular extrasystoles were noted at the time of the examination in only 4.6 per cent. I expected much more. I also expected that about 30 per cent of the subjects would have atrial fibrillation, but it was found in only 7.4 per cent. As it is such a common disturbance, this probably means that people with atrial fibrillation do not live as long as others. Further, the following changes were noted in 30 per cent of the subjects: slight depression or elevation of ST, and a low or inverted T wave. These alterations were to be expected, because some degree of abnormality of the coronary system is common in the elderly. The QT interval measures the electrical systole of the ventricles. In our series the corrected QT interval averaged 1.02, with a minimum of 0.8 and a maximum of 1.2 (only 1 subject).

The data on heart sounds and electrocardiograms may be useful in the inter-

pretation of current electrocardiograms. For instance, when we find a certain QT, we want to know whether or not it is normal. It should not be correlated with the average QT for all ages, but with the average for old people; the same holds true for the PR interval and for possible abnormalities.

I cannot as yet interpret all these data. They have to be completed, discussed, and evaluated. This is just the beginning of a longer study, which we hope will supply important information to be used by anyone examining an elderly person.

MODERATOR DACK: Thank you, Dr. Luisada.

I can vouch for the fact that these studies are new. This is probably the first time they have been reported.

The third speaker is Dr. John H. Bland. He will discuss an important feature of the treatment of heart disease in the aged, namely, the "*Problems of Edema and Electrolyte Disturbances in the Aged.*"

WATER AND ELECTROLYTE DISTURBANCES

DR. JOHN H. BLAND: A short talk of this type reminds me of the wise teacher who, upon answering a letter from one of his former students, apologized for writing such a long letter because he did not have time to write a short one. It is difficult to convey much detailed information about edema and water and electrolyte metabolism in a short time, but I shall try.

I should like, first, to discuss some characteristics of body fluid and electrolytes that are peculiar to the aged, and to present more recent developments of concepts of normal values. It is an interesting idea that geriatrics stands, during the past ten years or so, in about the same place that pediatrics stood at the turn of the century, in that a new set of normal values is being accumulated.

Body water: The total body water of the aging human subject undergoes a gradual decrease in volume with advancing age. The average for healthy males over age 60 is about 38 liters, compared to 43 liters for those under the age of 55. The average for females over age 60 is 25 liters, compared to 28–29 liters for those between the ages of 35 and 55 years.

Among males more than 60 years old, about 52 per cent of body weight is made up of water, compared to 58 per cent in younger men. In elderly women, about 42 per cent of the body weight is water, compared to 47 per cent in women from 35 to 55 years of age. Thus, water accounts for a lesser percentage of body weight as one grows older.

The intracellular volume of water gradually declines with aging. I have no impression that this is clinically significant. Measurements show that intracellular water declines, both absolutely and relatively, and that the decrease is steady and gradual. A shift of water occurs from the intracellular to the extracellular space. The shift is not detectable in a period of one or two years, but upon examining people in groups between the ages of 20 and 90 years, it becomes apparent. The intracellular water, then, decreases with advancing age, and the extracellular water gradually increases. Both starvation and aging are associated

with shrinkage or loss of cell water, and a relative increase in extracellular water volume.

Body electrolytes: I should like to outline a few changes in total body composition that represent the studies of many workers. With aging, there is a tendency toward a decrease in the *total amounts* (not concentrations, and not related to extracellular water) of potassium, magnesium, phosphorus and nitrogen—substances that are mainly intracellular in location. There is a trend toward an increase in the total amounts of sodium, chloride and calcium—electrolytes that are mainly extracellular in location. However, the *concentration* of electrolytes in the extracellular water of older persons remains about the same as in younger persons. In health there appears to be no change, though the concentration does change rapidly in disease.

The pH of extracellular water tends to decline slightly with aging, though not outside the range of normal.

Physical state of body water: Little is known about the physical state of the body fluid in general, and about how it exists in the aged compared to younger people.

If we cut across a normal piece of tissue such as muscle, and allow the blood to drain out, no other fluid escapes. The tissue looks moist, and we know it contains more than half its weight of water. Obviously, we are dealing with something that resembles a jelly, rather than a water-filled sponge. It has long been known that protoplasm is a gel, and apparently extracellular water is a gel. We are prone to think of it as water that splashes, or water that is held in the tissue like a sponge, but it is just as much a gel as is extracellular supporting tissue, or protoplasm within the cells.

The firmness of the gel depends upon the degree of polymerization, and the size of the molecule of ground substance or mucopolysaccharides. The greater the degree of polymerization, the greater the firmness. Simple increase in extracellular water (edema) is associated with a decrease in firmness or tendency for the gel to move toward a sol—more liquid and less solid.

Anyone who examines edema clinically finds a difference from one person to another when palpating edematous tissue. There is an obvious difference in feeling between the edema of myxedema, the edema of congestive heart failure, and the edema of nephrosis.

Small molecules diffuse rapidly through gels. For instance, hypertonic saline administered to any normal person reaches equilibrium in about twenty minutes. However, following injection of larger molecules (*e.g.*, inulin) which diffuse slowly through gels, equilibrium requires about five hours. There is some evidence that inulin diffuses and reaches equilibrium more rapidly in aging people (over age 60) than it does in younger people, suggesting increased permeability of the ground substance or mucopolysaccharides. We do not know what this change represents.

Factors in edema: Let us consider briefly some of the factors operative in producing edema as it occurs in all states, and try to relate each one to the geriatric patient.

Edema implies failure of excretion of sodium and water. The most important

site of loss of sodium and water from the body is the kidneys; therefore, the ultimate point at which they are held in the body is the kidney. Edema, then, implies that the kidneys have failed to excrete sodium and water, for either renal or extrarenal reasons.

Landowne, Shock, and others have shown a progressive increase in renal vascular resistance, a decrease in renal plasma flow, a decrease in the glomerular filtration rate, and a decrease in the clearance of para-aminohippurate in the aging person. Thus, substantial evidence exists that there is a progressive decrease in both glomerular and tubular function with aging. We may expect, therefore, abnormal handling of water and ions.

One consideration that always arises when one sees a patient with edema, is whether or not there is a decrease in the concentration of serum protein and, hence, a decrease in osmotic pressure. I see no reason to assume that the aged person would be more likely to become edematous for this reason than anyone else, in the absence of malnutrition.

Such events as an increase in venous pressure may lead to edema. There is no reason to assume that an increase in venous pressure occurs as a part of the aging process.

I am not sure how useful this piece of information is at the moment, but it is interesting that Mudge and Bradley showed ten years ago that upon constricting a belt placed around a patient's neck there was a decrease in the excretion of sodium. There followed a series of experiments in which cuffs were put around the neck, the arms, and the legs; when constricted, a decrease in the excretion of sodium and water occurred regularly. Such decreases are transient, however, and merely indicate that there is a sharp cutback in the excretion of sodium and water upon the production of venous congestion. For instance, quiet standing is associated with retention of sodium and water, and a tight cuff on the arm temporarily has the same effect. It should be emphasized that these changes are transient, because the body adapts itself to the situation. We have carried out venous congestion studies in 16 patients past the age of 60, in which the cuffs were placed on the legs. In this small series of aged persons, there was a reduction in sodium and water excretion, just as in younger people.

I see no reason to indict a change in capillary permeability as a cause of edema in older people. Increased protein content of edema fluid is no more apt to exist in the aged than in younger persons. Obstruction to lymphatic drainage is not peculiar to aging.

Humoral factors in edema (aldosterone): I know of no evidence to support the concept that the regulation of antidiuretic hormone is any different in the aged than in younger people. I should like to hear the comments of the other members of the panel on this point.

The most recent and interesting aspect of the regulation of sodium and water metabolism is that related to the adrenocortical hormone, aldosterone. I know of no studies in the aged to determine the normal output of aldosterone. Most persons between the ages of 20 and 60 years would be expected to excrete 1 to 4 micrograms a day. Excretion seems to be increased in all edematous states. However, both blood and urinary levels may be markedly increased also in non-

edematous conditions. Therefore, edema is not due solely to excess secretion of aldosterone.

Briefly, 3 known factors which increase the secretion of aldosterone are: 1) sodium restriction, 2) potassium loading, undertaken in order to increase the level of serum potassium, and 3) a decrease in some segment of the volume of the vascular compartment.

Therapy of edema: What can these things tell us with regard to the therapy and prevention of edema? There are 3 important considerations:

1) Rigid restriction of sodium should be avoided in the aged. They are in a different category than younger people. Restricting sodium sharply to 100 or 200 mg. daily is apt to activate the sequence of events characterized by increased production of aldosterone and ultimate edema, if the patient has a circulatory abnormality. If the circulatory system is intact, increased production of aldosterone does not necessarily cause edema.

2) When it is necessary to restrict sodium in the therapy of edema in the aged, a range of 3.5 to 5.0 Gm. daily is recommended. For diuresis, Diamox and mercury should be given alternately, rather than mercury and ammonium chloride continually. Diamox promotes the excretion of urine high in sodium and bicarbonate, increases the chloride concentration of extracellular water, and decreases bicarbonate. Mercury has almost the opposite effect. It induces excretion of a urine high in sodium and chloride, decreases the chloride concentration of plasma, and increases bicarbonate. Thus, they do complement one another. I suggest the use of mercury at three-day intervals, with Diamox in between. The effect of mercury lasts much longer (about twenty-four hours) than that of Diamox (about six hours). In our experience, there seems to be no advantage in giving Diamox continuously three times daily, or even daily.

During prolonged use of mercurial compounds for diuresis, it is important to administer ammonium chloride occasionally.

I hope that my remarks will spark some discussion.

MODERATOR DACK: Thank you, Dr. Bland.

The fourth member of the panel is Dr. Raymond Harris. He will summarize some of these points from a clinical aspect and discuss the "*Treatment of Cardiovascular Disorders in the Aged.*"

TREATMENT

DR. RAYMOND HARRIS: With only ten minutes in which to discuss the treatment of cardiovascular disorders in the aged, I cannot help recalling some lines from Longfellow's poem, "A Psalm of Life." He wrote:

"Art is long, and Time is fleeting,
And our hearts, though stout and brave,
Still, like muffled drums, are beating
Funeral marches to the grave."

As physicians interested in problems of the aged, we try to prolong the inevitable march to the grave.

The conquest of heart disease is now the principal focus of attack, since heart disease is the Number One killer of our people. Approximately 93 per cent of deaths from cardiovascular diseases are caused by arteriosclerosis and high blood pressure. Hypertension alone accounts for about 11 per cent of these deaths.

Successful treatment of heart disease in the aged is important and practical. Success depends upon the skillful diagnosis and evaluation of the patient's heart, general status and physiologic reserves, the art of the physician and, of course, the available drugs.

I shall present, first, some general principles and, second, some original experimental data obtained at the Ann Lee Home in Albany, New York, in cooperation with Dr. Luisada's laboratory and with Dr. Aravanis of Greece.

We have epitomized our thoughts on the treatment of cardiovascular disease of the aged in the phrase "Multiphasic Therapy of Cardiovascular Disorders in Geriatric Patients." In this field, therapy is based upon the principle that *an older person must be treated as a complete entity*, rather than as a person with a single specific disease. For example, an elderly person with congestive heart failure may be moderately anemic, malnourished, and hypertensive. He may live on the top floor of a tenement house but share a bathroom on the first floor. Obviously, proper treatment must be directed not only to the major heart disease but also to his associated medical and socio-economic problems.

The correction of anemia and vitamin deficiency, the replacement of deficient minerals, the elimination of infection, and the correction of urinary retention may benefit the patient just enough to enable him to regain a more normal cardiovascular status. This type of therapy requires a physician willing to make multiple diagnoses, to take the time to evaluate his patient's health assets and debits, and then to provide the best available total treatment by utilizing, in addition to sound medical treatment, the community resources including social, economic and educational facilities. We have coined a new term, "*Holiatry*," to express this concept wherein the physician mobilizes and uses all available community resources in the medical treatment of his patient. It is derived from the Greek words "*holos*" meaning whole, entire, or complete, and "*iatreia*" meaning healing or medical treatment. In other words, "Holiatry" is medical treatment of the whole.

Prevention is also important in the treatment of cardiovascular disorders in old age. Good health and preventive measures are most practical between the ages of 40 and 65 years. During this middle period of life, prevention of stress and strain, elimination of nervous tension, proper control of weight and diet, maintenance of sufficient physical activity, and the correction of bodily disorders will insure better cardiovascular health in old age and permit more of us to reach 100 years of age or more in good health.

Elderly patients can live for years despite a poor myocardium or arteriosclerosis. Many have adjusted to their physical condition and can perform routine activity without difficulty until some sudden, unexpected strain is placed upon them. Then, the weakest part gives way. Cardiac arrhythmias, pulmonary

emboli, and emotional shocks—such as the passing of a dear one—may produce cardiac failure or death. The mechanism is not well understood, but the disruption may occur through hormonal changes or other alterations which unbalance the patient's borderline physiologic homeostasis.

During the second half of life, with which we are concerned today, the primary cardiovascular problems are arteriosclerosis, hypertension, myocardial infarction, angina pectoris, congestive heart failure, senile heart disease, cerebrovascular accidents, and chronic myocardial disease produced by rheumatic, luetic, and other disorders during younger, and presumably happier, days. Of these, hypertension, coronary artery disease, and congestive heart failure are the most important. Endocrine dysfunction may also cause heart disease.

I should like now to present briefly some of our original data in these fields.

About six years ago, we began to study the long-term *effects of hydralazine on hypertension in older people*. We found that their blood pressure could be reduced without difficulty. The lowering of blood pressure in older people, if accomplished gradually and not precipitously, may benefit them without producing cerebrovascular accidents or coronary insufficiency. However, during hydralazine therapy, congestive heart failure developed in several patients, due to the increased tachycardia and work of the heart produced by the drug.

About then, we began work with reserpine, which we were the first to test in geriatric patients. Little need be said about *reserpine and the other Rauwolfia drugs*, since even the most conservative physicians accept their use in the treatment of hypertension and, even more important, in the field of mental disease, so often seen in older patients with cardiovascular disease.

The value of these drugs in the treatment of heart disease and hypertension can readily be proved statistically. The new drugs for hypertension, introduced in 1953 and 1954, are even now beginning to effect a dramatic lowering of the death rate from high blood pressure. Between 1952 and 1955, the national death rate from hypertension with heart disease declined 18 per cent. The death rate from hypertension without heart disease declined 14 per cent. Recent statistics published by one of the insurance companies show that the mortality among their industrial policyholders decreased 20 per cent during this period.

Hypertensive patients should be treated at all ages. We can treat those in the younger group more vigorously and use the stronger ganglionic-blocking agents, such as *Veratrum viride* derivatives, and Rauwolfia preparations. I shall not proceed with a full-fledged discussion of their use.

A low-salt diet is helpful. This is really all prophylactic treatment to reduce the ravages of hypertension that occur as people grow older. In the middle period of life, between 40 and 65 years of age, strong prophylactic and preventive measures should be applied to maintain and preserve normal health. In old age itself, treatment should be less vigorous and more gradual.

The Rauwolfia preparations are the best therapeutic measures we have. Treatment of any kind should be beneficial, gradual, and nonrestrictive. Little is to be gained by frightening the patient. In many instances, he has lived with his hypertension for years. One may be better off not to disturb him or his hypertension. However, I still think that moderate doses of Rauwolfia will

stabilize elevated blood pressure within safe bounds and prevent the dangerous swings produced in old age by sudden emotional crises or stresses, which, in turn, may produce the small or large strokes with which we are all too familiar.

Elderly patients do not tolerate precipitous changes in blood pressure. We must remember that any drug used to treat elderly people should work gradually. This applies not only to antihypertensive drugs, but to nitroglycerin as well. In addition to their effect on hypertension, Rauwolfia drugs have other beneficial physiologic effects which decrease the work of the heart. I utilize Rauwolfia preparations to improve the appetite, cardiovascular status, nutrition, and emotional outlook of cardiovascular patients. Again, we must treat the patient as a whole.

Coronary artery disease is a leading, if not *the* leading, cause of death and disability in old age. Rauwolfia preparations and other coronary vasodilators have improved the therapy of angina pectoris, but nitroglycerin remains the most useful drug in this field.

In conjunction with Dr. Luisada's laboratory, we recently obtained some interesting data on the cardiovascular effects of *nitroglycerin*. In this study, 100 patients between the ages of 50 and 90 years rested in a supine position for fifteen to twenty minutes. In each, we obtained a control electrocardiogram and the blood pressure reading. We then gave each patient $\frac{1}{150}$ grain of nitroglycerin sublingually, and five minutes later repeated the blood pressure reading and the electrocardiogram. To our amazement, we found that this commonly used amount of nitroglycerin had caused marked changes. The subjects were divided into normotensive and hypertensive categories. In the normotensive group, $\frac{1}{150}$ grain of nitroglycerin caused 40 per cent of the normal electrocardiograms to become abnormal. In the hypertensive group, approximately 25 per cent of the normal electrocardiograms became abnormal. In the others with abnormal electrocardiograms before nitroglycerin, the abnormalities usually became worse. On the basis of these findings, we decided that nitroglycerin in this particular dose exerted a deleterious effect on the heart, as shown in the electrocardiogram.

What is the mechanism of this effect? In patients in whom the electrocardiogram indicated deterioration, the blood pressure—particularly the diastolic pressure—had dropped and the pulse rate had increased. Nitroglycerin is not beneficial when given to patients in sufficient dosage to decrease the blood pressure and increase the pulse rate. Since the time of this study, we have recommended that smaller doses of nitroglycerin be used, in order to prevent these adverse effects. A small amount—perhaps $\frac{1}{300}$ or $\frac{1}{400}$ of a grain—should be given initially. This dose will probably have a beneficial effect on the angina. If not, then a larger dose can be used, but one must remember that nitroglycerin can harm as well as relieve. Perhaps some of the patients with coronary artery disease who suddenly drop dead, actually had only angina. They may have taken nitroglycerin like chocolate drops to relieve anginal pain, and the resulting fall in blood pressure and tachycardia were the real cause of the myocardial infarction. Nitroglycerin is one of the longest used and most helpful drugs available, but it may be dangerous.

As for *congestive heart failure*, it would be presumptuous to outline the complete treatment to this experienced group. It is important to keep in mind that many elderly people may continue for many years in a borderline compensated cardiac state. If no arrythmias are present, the heart will remain compensated until the occurrence of some sudden stress (such as an infection or arrhythmia) causes a relapse. It is important to treat elderly patients promptly and quickly before irreversible changes occur.

Our experience with various *digitalis preparations* has been good. The dosage must be large enough to obtain the desired effect. Older people, as a rule, do not require smaller doses of digitalis. Treatment must be individualized. In our hands, gitalin has been highly successful in the treatment of older people with congestive heart failure. Any other type of digitalis probably would be equally successful, if the physician has acquired skill in using it. At our Home, once we have digitalized patients and maintained them on a steady regimen, we can often discontinue the drug.

Metabolic disorders, avitaminosis, and malnutrition are common among older people. In treating elderly patients with cardiovascular disease, one must consider *èndocrine disturbances* such as hyperthyroidism and hypothyroidism. We recently had an interesting patient who was admitted with congestive heart failure and an enlarged heart. One look at this woman gave us the clue to the diagnosis, which had been missed previously. She had myxedema with massive pericardial effusion. She was treated with *triiodothyronine*; in fact, I think that she was the first older person with myxedema and pericardial effusion so treated. We started with the recommended dosage of 5 micrograms daily. The response was dramatic. Within five days the pericardial effusion had disappeared. The patient also improved clinically, undergoing the physical and mental changes that we associate with successful treatment of myxedema. Unfortunately, after the patient went home she exerted herself too much and died from coronary occlusion. Necropsy proved the diagnosis of myxedema resulting from Hashimoto's disease.

GENERAL DISCUSSION

MODERATOR DACK: I should like to start the discussion period by asking Dr. Luisada a question about blood pressure. *Did you state that, on the basis of your figures, the blood pressure did not seem to rise with increasing age? Does that agree with Master's figures?*

DR. LUISADA: I am not acquainted with Dr. Master's figures, but I should like to point out that they came from a questionnaire sent to physicians. Physicians in private practice see people who are ill and have troubles. In the Home for the Aged, we studied people who simply were old, whether or not they had troubles.

MODERATOR DACK: I believe that many of Dr. Master's figures were based on persons in Homes for the Aged. When I worked with him on this problem, at least in the initial phases, we obtained most of our data from such persons.

DR. LUISADA: But are not his total figures the result of random selection, so that they may be slanted?

MODERATOR DACK: Possibly. *Do you think that a blood pressure of 160/90 is normal for a man aged 60?*

DR. LUISADA: That is a very common blood pressure, but it should be considered to be due to minor pathologic changes. It is not truly normal.

MODERATOR DACK: What range of normal did you use?

DR. LUISADA: For systolic pressure, we used an upper limit of 140 mm. and a lower limit of 110 mm. in the male, and an upper limit of 125 mm. and a lower limit of 90 mm. in the female.

MODERATOR DACK: Dr. Landowne, you have studied blood pressure with increasing age. What is your view?

DR. LANDOWNE: I stand somewhere between Dr. Master and Dr. Luisada, which is a very good position. We have some figures from a small, selected group of 67 normal persons with no clinical evidence of cardiovascular disease. We measured blood pressure by direct arterial puncture. The systolic blood pressure in this group increased with age. (This is shown also in Master's data up to the age of 80, after which there was no further increase.) However, the increase averaged less than 5 mm. Hg per decade. This was only the peak pressure. The average increase in pressure throughout systole, which is when the heart is really compressing blood, was less than that—only 2 per cent per decade. Neither of these 2 pressure readings—peak or mean systolic—represents the pressure which, on the average, distends the arteries. The mean pressure, or the average pressure over the entire heart cycle, increased less than 1 per cent per decade. This increase was neither statistically nor clinically significant in this small, selected group.

Two factors tend to make it appear that blood pressure increases with age: 1) people in general or as one sees them in office practice include those who are surviving with high blood pressure, and 2) systolic pressure is not representative of mean pressure, and commonly the pulse pressure tends to widen. However, many persons, as Dr. Luisada said, reach advanced age with a normal blood pressure, both as measured by cuff and as considered from a hemodynamic standpoint.

DR. LUISADA: May I add one comment? In the past, I have seen people between the ages of 65 and 75 who stated that they had been taking stimulating and vasoconstricting drugs for many years because a physician thought that they had "low blood pressure." I usually found the blood pressure to be between 120 and 140 mm. systolic and 80 to 85 mm. diastolic, which I considered normal for them. Still, they thought they were "sick" people and continued to drug themselves with medicines which may have been harmful. This is an important point. The first physician mistakenly thought that around age 75 the blood pressure should be 170 or 175 and that, since it was only 140, the patient was sick.

MODERATOR DACK: Dr. Bland, have you any thoughts about blood pressure changes with increasing age?

DR. BLAND: I have wondered if the relative increase in total body sodium in

old people might play a part in the elevation of blood pressure. I know of no proof.

MODERATOR DACK: Do you think there is enough increase in sodium to cause hypertension as we see it in George Meneely's rats which were made hypertensive by feeding them salt over long periods?

DR. BLAND: No, I do not. However, it needs to be determined whether or not aldosterone production is increased in older people beyond what we consider normal for younger age groups. To my knowledge, this has not been determined.

MODERATOR DACK: Dr. Luisada, there are a few questions about the people who composed your study. Would you like to answer them?

DR. LUISADA: There is a series of questions.

"*What was the youngest and the oldest age?*" The youngest was 50 and the oldest, 110.

"*What was the average or mean age of all groups?*" I think it was in the neighborhood of 70 years. I cannot remember exactly.

"*Was the group hospitalized or ambulatory?*" They were in a Home for the Aged, which means they were hospitalized *and* ambulatory.

"*What was the average hemoglobin level?*" I do not have the data, so I cannot tell you. They have been collected and are being tabulated.

The last question is, "*What do you consider normal blood pressure?*" In the older person, any pressure between 110 and 160 mm. Hg systolic, which is not accompanied by clinical disturbance explained by the blood pressure itself, should be considered normal.

MODERATOR DACK: I see that everyone is interested in blood pressure today. Dr. Harris, *can you differentiate between essential and arteriosclerotic hypertension?*

DR. HARRIS: An elevation primarily of the systolic blood pressure with widening of the pulse pressure represents arteriosclerotic hypertension. If the systolic and diastolic blood pressures are elevated, so-called essential hypertension is present.

MODERATOR DACK: *Would you treat a patient with normal diastolic pressure and elevated systolic pressure?*

DR. HARRIS: Ordinarily, I would not. A number of years ago Dr. Wiggers, using his mechanical circulation pump, came to the conclusion that, with a systolic blood pressure of 200 mm. Hg and a diastolic pressure of 80 mm., a patient could have severe hypertension. On the basis of that work, one might treat the patient with such alterations in blood pressure. I usually treat the elderly patient with a diastolic blood pressure of 100 mm. Hg or more.

MODERATOR DACK: *Is the incidence of cerebrovascular accidents increased in patients with arteriosclerosis of the aorta and a high systolic and a normal diastolic pressure?*

DR. HARRIS: I have no figures on that. I am not overly concerned when I see a patient with only an elevated systolic blood pressure.

MODERATOR DACK: Dr. Landowne?

DR. LANDOWNE: I do not know whether I can answer your question, but I would guess that the incidence of cerebrovascular accidents is increased, simply because it is generally increased in persons who show this range of blood pressure.

This does not establish cause and effect. I agree that one treats the patient and not the systolic pressure. I am inclined to think of blood pressure, systolic and diastolic, in terms of the mean or average pressure—or, better still, this pressure in relation to flow—because a patient with hypertensive disease may have a "normal" pressure when cardiac output has been reduced. I would illustrate this by saying that the effect of sodium nitrite on a person with hypertension would not improve his hypertensive disease, but might lower his blood pressure by reducing the venous return to the heart.

In general, I would not treat patients who have only high systolic blood pressure. They are not ill, they do not have symptoms and they do not need treatment. One is likely to convert them into people who think that they have hypertensive disease by mentioning to them that their blood pressure is high or offering them treatment for it. I would rather err on that side, and avoid overtreating patients who simply have an elevation of systolic blood pressure.

DR. HARRIS: Dr. Dack, I should like to say one other thing. We have been discussing the normal blood pressure in old age. Actually, in our present state of knowledge, we do not know what normal old age is. If we are going to discuss the question, we probably should discuss it by saying: "*What is the blood pressure in old age?*"

DR. LANDOWNE: May I ask Dr. Luisada a question in that regard?

MODERATOR DACK: Certainly.

DR. LANDOWNE: Dr. Luisada began by saying that he had a group of normal subjects. I am glad that a question came from the audience as to the age range and distribution, because he starts to call people old at the age of 50.

These are "normal" people, and yet he tells us that there was a staggering incidence of electrocardiographic abnormality. This is true because he and Dr. Harris are experts in electrocardiography, and they can detect these alterations. Thirty per cent of the subjects had T wave abnormalities, and 6 per cent had old infarcts. He said that this was explainable because some degree of abnormality of the coronary system is to be expected. Furthermore, the QT interval should be correlated with old age and old people.

Although in one sense these were normal subjects, I hope Dr. Luisada also agrees with me that these people were not normal because many had coronary and other artery disease. They were normal simply from the standpoint that they had no complaints and were living to a ripe old age. This is a normal old person in one sense, but, to return to Dr. Harris's point, this is not freedom from coronary artery disease, arteriosclerosis, or even hypertensive disease.

Disorders such as these, which patients can tolerate and live with, are common in many older persons. The physician can bear the burden of recognizing that disease is present, without transferring details to the patient and exciting his concern.

Is the word you used earlier "Holiatry," Dr. Harris?

DR. HARRIS: Yes.

DR. LANDOWNE: I am still going to look for a more attractive word, but the concept is a good one.

DR. LUISADA: I agree with Dr. Landowne, so there is not much that I can add.

MODERATOR DACK: Dr. Bland, someone wants to know how you account for *the firmness of muscle tissue in some persons over age 65, and the flabbiness in others. Is it due to differences in fluid and electrolyte content?*

DR. BLAND: I do not know. I can only speculate. The total body composition in younger people is about as follows with regard to 3 fundamental parts—water, lean fat-free tissue, and fat. Our body weight comprises about 60 per cent water, 22 per cent lean fat-free tissue, and 18 per cent fat. Women are relatively more obese and have relatively less body water.

I am not entirely sure about this, but I think that in the well person who is chronologically old and has a number of manifestations such as skin changes, osteoporosis, loss of height, and pigmentation of the palmar creases, there is a relative gain in weight as the result of a combination of 2 factors—gain in fat, and loss of lean tissue. Flabby muscles in an aged person may be an indication that this type of change has begun. This gain of fat over lean tissue may continue for several years, and precede the accelerated aging process.

MODERATOR DACK: Dr. Landowne, you have performed some studies on *kidney function and fluid content with increasing age*. Have you any comments concerning Dr. Bland's observations?

DR. LANDOWNE: I am glad Dr. Bland presented his data, because the change in body composition is an interesting and striking finding, which our group has also observed. According to his data, total body water decreases and extracellular fluid increases slightly. The important thing is that the so-called cellular body water decreases with age. He also said that the total body mass tends to decrease with age. He appended the important fact that there is a relative, and probably absolute, increase in fat in most people. From our own studies, we also have come to the conclusion that most older people have acquired a greater proportion of fat.

There is a speculative interpretation of some of these findings—at least of the decrease in body water—which I should like to offer to you. The total peripheral circulatory resistance is the ratio between blood pressure and cardiac output. At rest, in our group of ostensibly clinically normal subjects, the cardiac output decreased strikingly with age. The blood pressure did not decrease, however, so that the resistance to perfusion of blood vessels increased with age. This increase in resistance was slightly above 1 per cent per year, on the average, which is about the same as the observed decrease in cardiac output per year.

The data on the decrease in the basal metabolic rate with age are based on oxygen consumption. Carbon dioxide production also declines with age, as does the cellular water (estimated from the difference between total body water and extracellular water). For these 3 indices of metabolically active tissue, the average age change is a decrement of about 0.6 per cent per year.

It seems, then, that the increase in resistance to perfusion of the vessels is greater than the amount of "shrinking" of the body. I use the word "shrinking" euphemistically to refer to a decrease in metabolically active protoplasm. Over-all, there is apparently a more marked decrease in the perfusion of tissues than in their function. This suggests that in some measure the decrease in function may be due primarily to the decrease in perfusion of the tissues.

Thus I come back to the point that there is a decrease in vascularity, and this decrease in vascularity can be one of the important causes of cell atrophy, since it lowers the proportion of active protoplasm compared to less active material. I think, Dr. Bland, that this is at least an hypothesis for the decrease in intracellular fluid that your data and the data from our laboratory show.

Although the decrease in flow relative to the decrease in metabolism is greater for the body as a whole, this may or may not apply in all regions or organs. It probably is also true for cerebral tissues, although here the data are equivocal. It is certainly true in the renal area. Other circulatory beds need to be observed to see whether, in our contemporary population, a decrease in vascularity precedes rather than follows a decrease in the number of metabolically active cells.

MODERATOR DACK: Apropos of that, it is perhaps pertinent to discuss at this point the matter of *physical activity*.

Some interesting work has been carried out at the Minnesota laboratories and abroad, which seems to indicate that physical activity will actually increase capillary vascularity and thus improve and aid the heart and other muscle tissue. Personally, I think every person should remain active as long as possible. The concept of rocking-chair rehabilitation is perhaps an important one. Even old people who cannot work or walk can at least rock themselves and in that way keep mobile.

DR. LANDOWNE: Dr. Hardin Jones has some interesting data which suggest that circulation through the muscles decreases rapidly, not only in the aged, but in adults who are growing older. This may be from disuse.

Dr. Keys's group has reported that a critical review of the relation of physical activity to coronary artery disease does not offer much support for the concept that physical activity is positively correlated with coronary artery disease. Thus, here are two good reasons to woo the rocking chair.

MODERATOR DACK: Are there any other comments from the panel members? If not, I wish to thank the members of the panel for an informative, provocative and scholarly discussion.

CHRONIC COR PULMONALE—ITS MANAGEMENT.

Notes on the Use of Chlorothiazide (Diuril)

MAURICE S. SEGAL, M.D.,* ERNST O. ATTINGER, M.D.† and JALE DUVENCI, M.D.‡

The Department of Medicine, Tufts University School of Medicine, and Lung Station (Tufts), Boston City Hospital, Boston, Massachusetts

Chronic cor pulmonale, also referred to as pulmonary heart disease and pulmono-cardiac failure, may be defined as heart disease secondary to disease of the lungs or their blood vessels. The primary pulmonary disease must be such that it interferes with the passage of blood through the pulmonary circuit, thereby putting an undue strain upon the right chambers of the heart. Interference with blood flow may occur anywhere between the pulmonic valve and the left atrium and is believed to originate usually either in the pulmonary arterial tree or capillary bed, primary obstruction of venous flow in humans being rare. Although chronic cor pulmonale has been invariably bound to pure right ventricular hypertrophy, in many instances the left ventricle and the systemic circulation are likewise involved (1).

The incidence of chronic cor pulmonale is from 5 to 10 per cent of all forms of heart disease. The patients are usually in the age range of 40 to 60 years, and males predominate. Chronic bronchitis with emphysema is the commonest cause of chronic cor pulmonale (2).

CLINICAL MANIFESTATIONS

The development of chronic cor pulmonale is usually insidious. Unfortunately, it is generally not recognized until frank right ventricular failure supervenes.

The *very early* clinical manifestations of chronic cor pulmonale are in essence the signs and symptoms of the underlying chronic bronchitis and chronic pulmonary emphysema. Clinical awareness of the manifestations of pulmonary hypertension associated with either a low or increased cardiac output may lead to early recognition. Confirmation can be made with the aid of right cardiac catheterization by the demonstration of pulmonary hypertension associated with diminished or increased cardiac output. *A high index of suspicion of the diagnosis of chronic cor pulmonale in patients with chronic pulmonary emphysema with persistive cough, dyspnea and cyanosis is always advisable.* The patient, although dyspneic, is usually able to sleep in a normal position and does not complain of

* Clinical Professor of Medicine, Tufts University School of Medicine, and Director, Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital.

† Research Fellow, American Heart Association; Assistant Professor in Medicine, Tufts University School of Medicine; Research Associate, Lung Station (Tufts), Boston City Hospital.

‡ Chief Resident, Department of Inhalation Therapy, Boston City Hospital, and Research Fellow in Medicine, Tufts University School of Medicine.

orthopnea. Changes in the electrocardiogram, roentgenogram, venous pressure and circulation time appear only when the disease is clinically well established. During this early phase compensatory hyperventilation may frequently be noted, appearing in untoward episodes induced by bronchoconstriction, infection or exercise.

The *later* manifestations of pulmono-cardiac complications are essentially those due to chronic pulmonary hypertension, hypertrophy, dilatation, failure of the right heart and the superimposed effects of chronic hypoxia. Cyanosis of the lips, buccal mucosa and fingertips, and clubbing of the fingers may develop or become more pronounced. Cardiac dilatation is generally, although not invariably, associated with increased cardiac output; the next stress on the trigger mechanism may initiate failure. This can occur as a result of exercise, respiratory infection, bronchiolar obstruction or other clinical states associated with increased metabolic rates.

The clinical manifestations in the *advanced stage* are easy fatigability, exertional dyspnea, orthopnea and cyanosis. There may be evidence of congestive failure, *i.e.*, a tender or enlarged liver, distended neck veins, increased venous pressure, peripheral edema and ascites. The cardiac rhythm and blood pressure tend to remain unchanged if the systemic circulation does not participate in the pathologic process. The pulmonic second sound is accentuated and is usually greater than the aortic second sound. The chest roentgenogram, fluoroscopic picture, and the electrocardiogram show evidence of right ventricular hypertrophy or enlargement. The ability of the right ventricle to hypertrophy in order to meet the increased load is most impressive.

PATHO-PHYSIOLOGY

In chronic pulmonary emphysema, a progressive disruption of alveolar septa and obliteration of the pulmonary vascular bed occurs. This results in an inefficient distribution of blood and gas in the lungs, due to perfusion of poorly ventilated alveoli and ventilation of poorly perfused alveoli (2) (dissociation of the normal ventilation-perfusion ratio). In the early stages, normal arterial oxygen saturation is maintained and carbon dioxide retention is prevented by hyperventilation. When adequate compensation for the early disturbances in ventilation and perfusion (and ultimately in diffusion) cannot be maintained, there is a drop in arterial oxygen saturation and carbon dioxide retention, and chronic respiratory failure is evident. Sudden disturbances in the mechanics of breathing, such as evoked by strenuous physical effort, respiratory infections, bouts of bronchoconstriction or increased metabolic rates, accelerate the development of respiratory failure; and when the latter is already manifest, they hasten the appearance of right ventricular failure.

The relationship of pressure and flow in the pulmonary vasculature is quite different from that in the systemic circulation, the mean pressure in the aorta being approximately six times higher (100 mm. Hg) than that in the pulmonary artery (15 mm. Hg). This is due to the high resistance to blood flow in the systemic arterioles, the walls of which are supplied with a vast amount of smooth,

circular musculature. In contrast, the muscular supply of the pulmonary arterioles is fairly small.

The pulmonary vasculature in normal subjects is a highly distensible, low-pressure system. The cardiac output can increase up to threefold without a concomitant increase in pressure in the pulmonary artery (Table 1). An increase in transmural pressure leads to an increase in the vessel diameter until the elastic limit of the vessel wall is reached. For a given flow rate the driving pressure varies inversely to the fourth power of the vessel radius, and pulmonary vascular resistance decreases markedly as the transmural pressure rises, until a plateau is reached. At this point the vasculature behaves like a rigid system. With increasing flow rates, the pulmonary vascular resistance decreases, partly because of a decrease in apparent viscosity of the blood and also because of an increase in the size of the vessel (3, 4). Comparison and interpretations of pulmonary vascular resistance, therefore, have to be made with caution if they are not based on comparable transmural pressures and flow rates. Furthermore, the driving pressure across the pulmonary vascular bed represents the difference between mean pulmonary artery (P.A.) pressure and mean left auricle (L.A.) pressure. Pulmonary capillary pressure (wedge pressure) is not always a reliable substitute for L.A. pressure, particularly when measured after the administration of drugs and in mitral stenosis. It has also been shown that with changes in pulmonary mechanics or hemodynamics, there is frequently a dissociation between the change in blood pressure in various segments of the vasculature and the change in intrathoracic blood pressure (5). Thus, an apparent decrease in P.A. pressure may actually represent an increase, when the transmural P.A. pressure is considered.

Figure 1 shows the changes in diastolic pressure and pulse pressure occurring in the brachial artery and in the right ventricle, recorded simultaneously with the changes in intrathoracic pressure associated with respiration. In the right ventricle there was a drop in pressure with inspiration and a rise with expiration. This reflected itself throughout the pulmonary vasculature. In Figure 2 it will be seen that during the Valsalva maneuver in a patient with chronic pulmonary emphysema, the right ventricular pressure rose about 48 cm. of water as com-

TABLE 1. *Hemodynamic Changes in a Normal Subject (N.) and a Patient (P.H.T.) with Pulmonary Hypertension during Exercise*

Cardiac Output (L./min.)	Mean Pressure (mm. Hg)				PVR* (dyn./sec. cm.$^{-5}$)		RVW† (Mkg./min.)		LVW‡ (Mkg./min.)	
	Brachial artery		Pulmonary artery							
	N.	P.H.T.	N.	P.H.T.	N.	P.H.T.	N.	P.H.T.	N.	P.H.T.
5	100	100	10	31	160	500	0.68	2.11	6.8	6.8
10	100	100	10	63	80	500	1.36	8.6	13.6	13.6
15	100	100	12	94	64	500	2.45	19.2	20.8	20.8

* Pulmonary vascular resistance.

† Right ventricular work (meter kilograms per minute).

‡ Left ventricular work (meter kilograms per minute).

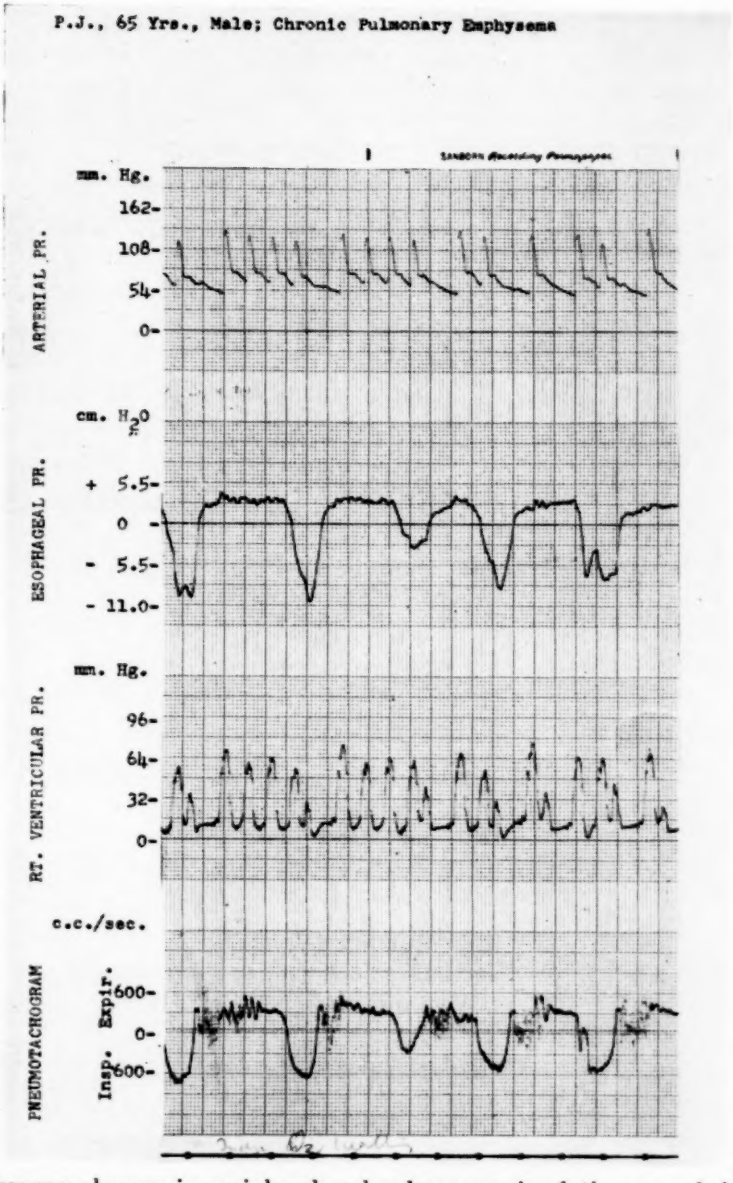

FIG. 1. Pressure changes in peripheral and pulmonary circulation recorded simultaneously with intrathoracic pressure changes in a patient with chronic pulmonary emphysema during oxygen breathing. Note marked ball-valving in expiratory flow pattern.

pared to 26 cm. in the intrapleural space. Thus, the net increase in diastolic right ventricular pressure was only 22 cm. of water. This rise in intrathoracic pressure offset partly the rise in pulmonary vascular pressure, thus preventing possible pulmonary edema. From the decrease in pulse pressure, one may infer that the cardiac output decreased markedly. Because of the non-linear pressure flow relationship, the pressure gradient across the pulmonary vascular bed remained relatively constant in spite of varying flow rates.

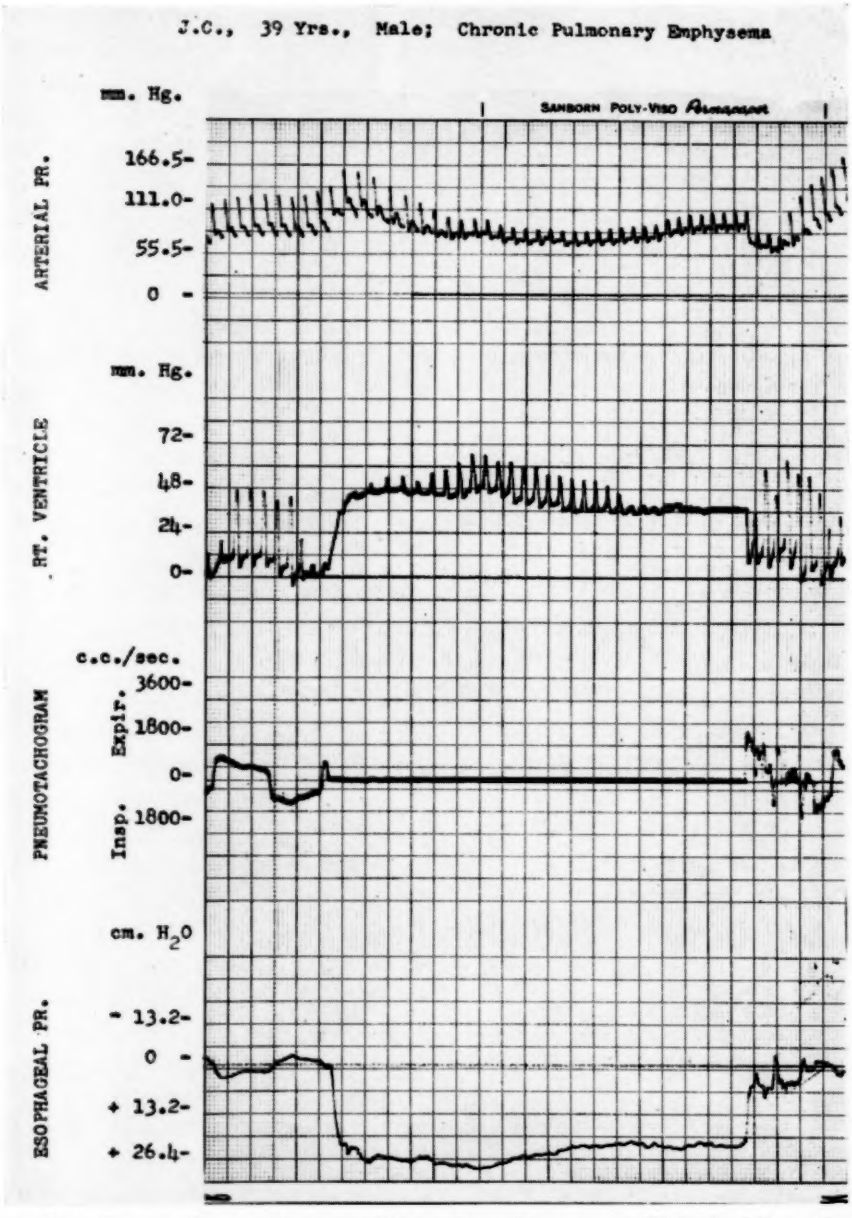

FIG. 2. Circulatory effects of increased intrathoracic pressure (Valsalva) in patient with chronic pulmonary emphysema.

In patients with chronic pulmonary disease, pulmonary hypertension follows in the wake of either primary pulmonary vascular disease (essential pulmonary hypertension) or alveolar hypoventilation (6, 7). In the latter condition, pulmonary hypertension is provoked by low oxygen tension and/or high carbon dioxide tension, and is, at least in the beginning, reversible by improving the alveolar ventilation. If anoxia and hypercapnia persist, pulmonary hypertension becomes fixed because of progressive reduction in the capacity of the pulmonary vascular

bed, leading to pulmonary vascular sclerosis—comparable in a way to the peripheral arteriosclerosis in systemic hypertension.

At this stage, most of the vasculature is already in use even at rest and there is no reserve for states in which the flow rates are increased, notably during exercise, fever or increased metabolic demands. Pulmonary arterial pressure rises considerably under these conditions and may rise further by increases in cardiac output in response to effort (8). Thus, pressure in the pulmonary artery changes proportionately with blood flow, the pulmonary vascular resistance being elevated and relatively fixed.

The limited capacity of the vascular bed under these conditions is borne out further by the fact that the diffusion capacity does not rise during exercise. This means that the amount of blood coming in contact with the alveolar air per unit time remains constant. Because pulmonary vascular resistance is elevated in pulmonary hypertension, an increase in cardiac output must lead to a greater increase in right ventricular work than in patients with normal pulmonary artery pressure. Thus, in the presence of increased pulmonary vascular resistance, the possibility of increasing the cardiac output during exercise is limited. The augmented peripheral need for oxygen must be met by increased extraction of oxygen from the arterial blood, *i.e.*, an increased arterio-venous oxygen difference. Because there is a limit to the reduction of venous oxygen concentration (pO_2) the oxygen-carrying capacity of the blood increases by means of secondary polycythemia. Unfortunately, the polycythemia adds further to the distress of the myocardium by increasing blood volume and blood viscosity. Associated reduction in arterial oxygen saturation, elevation of hematocrit, abnormal pulmonary ventilation function, normal platelet and white blood cell counts and absence of a palpable spleen help to differentiate the polycythemia of chronic cor pulmonale from polycythemia rubra vera.

If during exercise the pulmonary blood volume increases (pulmonary congestion, left heart failure), an additional load is imposed on the right ventricle. The pulmonary vascular resistance is expressed as follows:

$$\text{PVR} = \frac{\text{PAP}_{(\text{mean})} - \text{LAP}_{(\text{mean})}}{\text{C. O.}} \times 80 \text{ dyn./sec. cm.}^{-5}$$

and right ventricular work:

$$\text{RVW} = \frac{\text{PAP}_{(\text{mean})} - \text{RAP}_{(\text{mean})}}{1000} \times \text{C. O.} \times 13.6 \text{ Mkg./min.}$$

To illustrate the foregoing, we have calculated the changes occurring in pulmonary vascular resistance (PVR), pulmonary arterial pressure (PAP), right ventricular work (RVW) and left ventricular work (LVW) during an increase in cardiac output (C.O.) such as might occur during exercise for a normal subject (N.) and a patient with moderate pulmonary hypertension (P.H.T.) (Table 1). A mean brachial artery pressure of 100 mm. Hg has been assumed.

It will be seen that in the normal subject (Table 1) right ventricular work (RVW) increased proportionately to cardiac output while pulmonary vascular

resistance (PVR) decreased with increasing cardiac output. The ratio of RVW to LVW remained constant. In contrast, in the patient with pulmonary hypertension the pulmonary artery pressure (PAP) increased in proportion to cardiac output (C.O.), and the right ventricular work (RVW) in proportion to the product of C.O. and mean PAP, the RVW reaching approximately the level of the LVW at a C.O. of 15 liters per minute.

Because the right ventricle is especially suited to the task of pumping large or widely varying volumes of blood against a low outflow pressure, it has to adapt itself to chronic rises in PA pressure by developing thick walls and a more cylindrical shape, thus assuming some of the characteristics of the left ventricle (9). Sudden increases in outflow pressure frequently lead to death, because the right ventricular myocardium is unable to sustain the higher pressures needed to provide adequate flow through the lung.

The combined effects of the primary pulmonary disorder and the secondary cardiac disorder are included in the terms pulmonary heart disease or chronic cor pulmonale. The prevention of chronic cor pulmonale depends largely upon the early recognition of the underlying pulmonary disease and the correction of the associated bronchial constriction, bronchial or parenchymal infections, pulmonary hypertension, hypoxia, carbon dioxide retention or ventilatory defects.

When myocardial degeneration develops or when the optimal stretch of the myocardial fibers has been exceeded, the increased cardiac output begins to fall. Nevertheless, it still may be greater than normal, even in the presence of congestive failure. *Compensatory hyperventilation is largely lost in these patients and hypoventilation is more common.* In patients with severe degrees of arterial hypoxia there is a tendency toward respiratory acidosis, marked polycythemia and hypervolemia, severe pulmonary hypertension, high cardiac output with or without failure and a marked elevation of diastolic pressure in the right ventricle (10–12). In these last stages, the pulmonary hypertension is irreversible and is accompanied by intractable heart failure. As a rule, these patients seldom recover full compensation and usually succumb in a few months.

TREATMENT

If a patient with chronic cor pulmonale can be tided over a crisis, especially if there is cardiac failure which appears at the moment to be due largely to respiratory components, the physician will be rewarded and even amazed by the subsequent improvement, which may persist for months or even years. If the patient's condition is primarily cardiac, his outlook is usually not so favorable but, with careful management, improvement may be maintained for a surprising length of time.

The best treatment of chronic cor pulmonale is preventive. Among the useful aids to be discussed in the interim management of the patient with underlying chronic pulmonary emphysema are aminophyllin, bronchodilator aerosols, antimicrobial agents, diaphragmatic breathing exercises, emphysema belts, periodic venesection when indicated, and intermittent positive-pressure breathing with simultaneous bronchodilator sprays. Steroids may be of value in patients with

repeated bronchospastic crises. Particular attention should be paid to the prevention and early recognition of the respiratory acidosis which may follow in the wake of over-zealous use of barbiturates, opiates and high concentrations of oxygen, particularly when used in combination (an unfortunate form of "therapeutic kindness").

The management of cardiac failure in chronic cor pulmonale is similar in many respects to that of any type of heart failure. However, attention must be paid to the management of the underlying etiologic disorders, particularly the associated bronchoconstriction and infection. Prevention of alveolar hypoventilation, chronic hypoxia and respiratory acidosis may eliminate troublesome "trigger" mechanisms. For the treatment of heart failure, restricted physical activity, and the judicious use of oxygen, digitalis, salt restriction, oral or parenteral mercurial compounds and oral diuretics are indicated, more or less in that order.

A strict program of weight reduction must be undertaken in the massively obese patient in order to correct the alveolar hypoventilation and the events which follow in its wake, namely, hypoxia, respiratory acidosis, pulmonary hypertension and chronic cor pulmonale (Patient No. 18, Table 2).

Additional measures that are specific for the underlying pulmonary disease in most patients with chronic cor pulmonale include aminophyllin, bronchodilator aerosol therapy and phlebotomy.

The results of treatment (with special reference to the use of chlorothiazide as a diuretic) in 23 patients with chronic cor pulmonale are shown in Table 2.

Aminophyllin

Aminophyllin is a safe, reliable drug for the management of patients with chronic cor pulmonale. It has a relaxing action upon the bronchioles and upon the pulmonary vasculature as well (12). When given in adequate amounts, it decreases the resistance to air flow into and out of the lungs. Thus, the induced increase in the rate of air flow is not accompanied by a corresponding increase in the transpulmonary pressure gradient. Because resistance to air flow decreases and pulmonary compliance increases, the work of breathing is reduced (Fig. 3). Clinically, aminophyllin diminishes wheezing and lessens the respiratory efforts of the patient. Because of this and possibly also because of a direct effect upon the pulmonary blood vessels, it decreases resistance to blood flow through the lungs and lessens the work of the right ventricle. An impressive diminution of pulmonary arterial pressure may be achieved as a consequence of decreasing the resistance in the pulmonary circuit. Aminophyllin can serve as a means of evaluating the degree of reversibility of pulmonary hypertension. Lack of response indicates a poor prognosis. Notable improvement in Cheyne-Stokes respirations may also be observed after intravenous administration of aminophyllin.

An adequate blood level of aminophyllin is best maintained by administration of the drug intravenously by continuous slow drip at a rate of 30 drops per minute, providing 0.5 Gm. of aminophyllin in a liter of 5 per cent glucose in water every eight hours. A total of 3 liters of fluids intravenously in twenty-four hours may be administered in the presence of adequate total output. Seriously

TABLE 2. *Summary of Data on 23 Patients with Chronic Cor Pulmonale Treated with Diuril*

Case No.	Patient Name, Age, Sex	Diagnosis*	Previous Therapy†	Diuril‡	Comments	Results
1	S.R., 66 M	C.B. C.B.A. C.P.E. C.C.P.	Dig. A.m.A. B.d.A. Merc. Hosp. R.	Nov. 25/57–Jan. 15/58, 250 mg. t.i.d. Jan. 15/58, reduced to 250 mg. d.	No shortness of breath; wt. loss, 13 lbs.; omitted merc. wkly. inj.; required less B.d.A.; weakness after 2 wks. overcome c̄ more salt p.o.	Good. No need for merc.
2	H.H., 56 F	Sev.H.B.P. C.B. C.B.A. C.P.E. C.C.P.	Dig. A.m.A. B.d.A. Merc. Hosp.	Nov. 20/57–Jan. 21/58, 500 mg. q.i.d. Jan. 21/58, reduced to 500 mg. b.i.d.	Wt. loss, 4 lbs.; B.P. 170/100, stabilized from 220/130; excell. diuresis; fewer headaches.	Good. Drop in B.P.; relief from headaches.
3	J.T., 63 F	C.B. C.B.A. C.P.E. C.C.P.	Dig. A.m.A. B.d.A. Merc.	Dec. 11/57–Feb. 20/58, 500 mg. q.i.d. Feb. 20/58, reduced to 500 mg. b.i.d.	Wt. loss, 15 lbs.; excell. diuresis; no need for merc.; no shortness of breath.	Good. No need for merc.
4	J.B., 73 M	Sev.H.B.P. C.B. C.B.A. C.P.E. C.C.P.	Dig. A.m.A. B.d.A. V. R.	Oct. 28/57–Jan. 17/58, 500 mg. t.i.d. Jan. 17/58, reduced 500 mg. b.i.d.	Wt. loss, 4 lbs.; B.P. dropped to 210/92 from 260/110; good diuresis; less shortness of breath.	Good. Drop in B.P.; less shortness of breath
5	R.L., 50 F	C.B. C.B.A. C.P.E. C.C.P.	Dig. A.m.A. B.d.A. Diur.	Nov. 2/57–Feb. 1/58, 250 mg. t.i.d. Feb. 1/58, increased to 500 mg. t.i.d.	Less shortness of breath; less need for B.d.A.; trial c̄ higher dosages (persistent leg edema); felt better.	Good. Less shortness of breath; reduced need for B.d.A.
6	J.P., 55 M	C.B. I.P.F. C.C.P.	Dig. A.m.A. Diur.	Nov. 9/57–Feb. 8/58, 250 mg. t.i.d. Feb. 8/58, reduced to 250 mg.	Wt. loss, 7 lbs.; less shortness of breath.	Good. Less shortness of breath.

6	J.P., 55 M	C.B. I.P.F. C.C.P.	Dig. A.m.A. Diur.	Nov. 9/57–Feb. 8/58, 250 mg. t.i.d. Feb. 8/58, reduced to 250 mg. b.i.d.	Wt. loss, 7 lbs.; less shortness of breath.	Good. Less shortness of breath.
7	B.S., 55 F	C.B. C.B.A. C.P.E. C.C.P.	Dig. A.m.A. B.d.A. Diur. Ster. Hosp.	Nov. 2/57 to date, 250 mg. t.i.d.	Wt. loss, 5 lbs.; subsiding leg edema; less shortness of breath.	Good. Less shortness of breath; reduced need for B.d.A.
8	N.B., 50 M	Sev. K.S. p̄ Polio C.C.P. R.A. Hosp.	Dig. O_2 Ven. Diur. A.m.A.	Nov. 1957, I.V., 500 mg. b.i.d.-t.i.d.; then orally, 250 mg. b.i.d.	Excell. diuresis; supplementary program of IPPB c̄ B.d.A., low conc. O_2 & A.m.A.; comatose at outset; recovered c̄ return of arterial blood gases to normal range.	Good. *Intravenous use.*
9	S.L., 76 F	C.B. P.F. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. Ster. Diur. Merc.	Nov. 20/57 to date, 250 mg. t.i.d.	Wt. loss, 5 lbs.; good diuresis; leg edema subsided; B.P. dropped to 150/100 from 170/110; less shortness of breath.	Good. Drop in B.P.; less shortness of breath.
10	R.S., 73 F	C.B. C.B.A. C.P.E. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. Ster. R.	Nov. 30/57–Dec. 30/57, 500 mg. t.i.d.	B.P. dropped to 170/100 from 196/110. Good diuresis; less "steroid" mooning & leg edema noted. Omitted p̄ 1 month because of anorexia & G.I. upset.	Fair. Drop in B.P.; less edema.
11	J.M., 62 F	C.B. C.B.A. C.P.E. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. Ster. R. V. Merc.	Dec. 4/57 to date, 500 mg. t.i.d.	Wt. loss, 3 lbs.; B.P. dropped to 160/100 from 190/100; less shortness of breath; less "steroid" mooning of face; less leg edema; required fewer Rx's.	Good. Drop in B.P.; less shortness of breath; less edema; fewer Rx's required.

TABLE 2.—*Continued*

Case No.	Patient Name, Age, Sex	Diagnosis*	Previous Therapy†	Diuril‡	Comments	Results
12	J.F., 66 M	C.B. C.B.A. C.P.E. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. Ster. Merc.	Dec. 4/57 to date; 500 mg. t.i.d.	Wt. loss, 3 lbs.; less shortness of breath; less leg edema; B.P. dropped from 190/110 to 150/100; less need for merc.	Good. Drop in B.P.; less shortness of breath; less edema.
13	F.K., 60 M	C.B. C.B.A. C.P.E. C.C.P.	Dig. A.m.A. B.d.A. Merc.	Dec. 4/57 to date, 500 mg. t.i.d.	Wt. loss, 4 lbs.; less shortness of breath; less leg edema; less need for merc.	Good. Less shortness of breath; less leg edema.
14	P.T., 58 M	C.B. C.B.A. C.P.E. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. Diur. R. Merc.	Dec. 6/57 to date, 500 mg. t.i.d.	Wt. loss, 10 lbs.; B.P. dropped to 150/88 from 170/100; less shortness of breath; less leg edema; no further need for merc. wkly.	Good. Drop in B.P.; less edema; no need for merc.
15	J.D., 80 M	P.F. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. Diur. R. Merc. Ster.	Dec. 20/57–Jan. 20/58, 500 mg. b.i.d. Jan. 20/58 to date, 250 mg. b.i.d.	B.P. dropped to 120/55 from 150/65; less leg edema; no need for merc. twice wkly.; less shortness of breath.	Good. Drop in B.P.; less edema; no need for merc.
16	M.F., 62 F	C.B. C.B.A. C.P.E. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. Diur. R. V. Ster.	Jan. 15/57 to date, 250 mg. t.i.d.	Wt. loss, 3 lbs.; B.P. dropped to 170/100 from 200/100; less leg edema; less shortness of breath; fewer Rx's needed.	Good. Drop in B.P.; less shortness of breath; fewer Rx's required.
17	S.O., 65 F	C.B.A. C.P.E.	Dig. A.m.A.	Dec. 10/57 to date, 500 mg. b.i.d.	B.P. dropped to 150/90 from 182/90; less edema; fewer	Good. Drop in B.P.; less

			Ster.			
17	S.O., 65 F	C.B.A. C.P.E. C.C.P. H.B.P.	Dig. A.m.A. B.d.A. R. V. Ster.	Dec. 10/57 to date, 500 mg. b.i.d.	B.P. dropped to 150/90 from 182/90; less edema; fewer Rx's needed.	Good. Drop in B.P.; less edema; fewer Rx's required.
18	I.K., 47 M	C.B.A. C.P.E. C.C.P. H.B.P. Obesity R.A. C.H.F.	Dig. A.m.A. B.d.A. R. V. Ven. Many hosp. Diur. Merc.	Nov. 21/57–Jan. 21/58, 500 mg. q.i.d. Jan. 21/58–Feb. 21/58, 500 mg. b.i.d. Feb. 21/58 to date, 500 mg. d.	Critically ill (C.H.F., H.B.P. obesity and C.B.A.), treated c O_2, Dig., Merc., A.m.A. etc. Wt. loss from Apr. '55 to Feb. '58—447 lbs. to 247 lbs.; striking improvement in CO_2 retention synd.; required merc. 2x wkly. & other diuretics p.o.; since Nov. 21/57, progressive omission of all other diuretics; B.P. stabilized at 200/100 from 260/130.	Good. No need for merc.; wt. & B.P. stabilized; less need for other Rx's.
19	A.W., 64 M	A.S.H.D. C.H.F. C.P.E.	Dig. Diur. L.S.D. Ngl. B.d.A.	Nov. 27/57–Dec. 29/57, 500 mg. q.i.d. Jan. 3/58–Mar. 26/58, 500 mg. d. Mar. 27/58–Apr. 2/58, none Apr. 2/58, started 250 mg. b.i.d.	Free of edema; discont'd Diuril due to nausea. Tolerated this dosage well; free of edema; electrolytes normal; wt. stable. Recurrent, marked ankle edema.	 Good. Good.
20	M.R., 68 M	C.B. B.ect. C.P.E. C.C.P.	Dig. Diur. B.d.R. B.d.A. L.S.D.	Dec. 9/57–Dec. 31/57, 500 mg. b.i.d. Dec. 31/57–Jan. 8/58, 250 mg. b.i.d. Jan. 8/58–Jan. 17/58, 500 mg. to 250 mg. d. Apr. 18/58 to date, 250 mg. b.i.d.	Free of edema; wt. loss, 11 lbs.; intermittent nausea. Sl. recurrent edema & wt. gain of 5 lbs.; no nausea; increasing dyspnea on exertion. Wt. gain continued; recurrent nausea; back to Rolicton therapy; hospitalized. This dosage of Diuril tolerated well; patient responded.	Marked G.I. upset with large doses. Good. (with lower dosage).

TABLE 2.—*Continued*

Case No.	Patient Name, Age, Sex	Diagnosis*	Previous Therapy‡	Diuril‡	Comments	Results
21	A.D., 60 M	C.B. C.P.E. C.C.P.	Dig. L.S.D. B.d.R.	Feb. 24/58–Apr. 9/58, 250 mg. b.i.d. Apr. 9/58 to date, 250 mg. b.i.d., 6 days/wk.	Diuril started when paroxysmal noct. dyspnea appeared; patient relieved in 1st wk. of Rx.; well since; electrolytes normal. No recurrence of PN dyspnea; free of edema	Good.
22	W.M., 54 M	C.B. C.P.E. P.F. C.C.P. B.P.H.	Dig. B.d L.S.D.	Feb. 24/58–Mar. 24/58, 250 mg. b.i.d. Apr. 23/58–Apr. 30/58, none. Apr. 30/58 to date, 250 mg. b.i.d.	Diuril started when paroxysmal noct. dyspnea appeared; patient relieved in 2nd week; electrolytes normal within 2 wks. after start of Rx No Diuril for 1 wk. Free of edema; no wt. gain.	Good.
23	T.Mc., 74 M	C.B.A. C.P.E.	Dig. B.d.R. B.d.O.	Apr. 18/58–May 3/58, 250 mg. b.i.d. May 2/58 May 13/58–June 3/58, none June 3/58 to date, 250 mg. b.i.d. June 10/58	Diuril started when pt. developed mild peripheral edema; 12-lb. wt. gain in 2 wks. Two wks. later—no edema. Nausea Recurrent leg edema. Lost 4 lbs.; edema well controlled.	Fair.

CODE

*C.B.	= Chronic Bronchitis	†Dig.	= Digitalis	‡ Orally, unless otherwise stated.
C.B.A.	= Chronic Bronchial Asthma	A.m.A.	= Antimicrobial Agents	
C.P.E.	= Chronic Pulmonary Emphysema	B.d.A.	= Bronchodilator Aerosols	
C.C.P.	= Chronic Cor Pulmonale	Merc.	= Mercurial Injection	
Sev.H.B.P.	= Severe High Blood Pressure	R.	= Rauwiloid	
Sev.K.S.	= Severe Kyphoscoliosis	V.	= Veriloid	
p̄ Polio	= After Poliomyelitis	Diur.	= Oral Diuretics	
R.A.	= Respiratory Acidosis	R.Am.	= Rectal Aminophyllin	
Hosp.	= Required Hospitalization	O.Am.	= Oral Aminophyllin	
P.F.	= Pulmonary Fibrosis	Ven.	= Venesection	
C.H.F.	= Congestive Heart Failure	Ster.	= Steroids	
A.S.H.D.	= Arteriosclerotic Heart Disease	L.S.D.	= Low Salt Diet	
Br.ect.	= Bronchiectasis	Ngl.	= Nitroglycerin	
		c̄	= With	

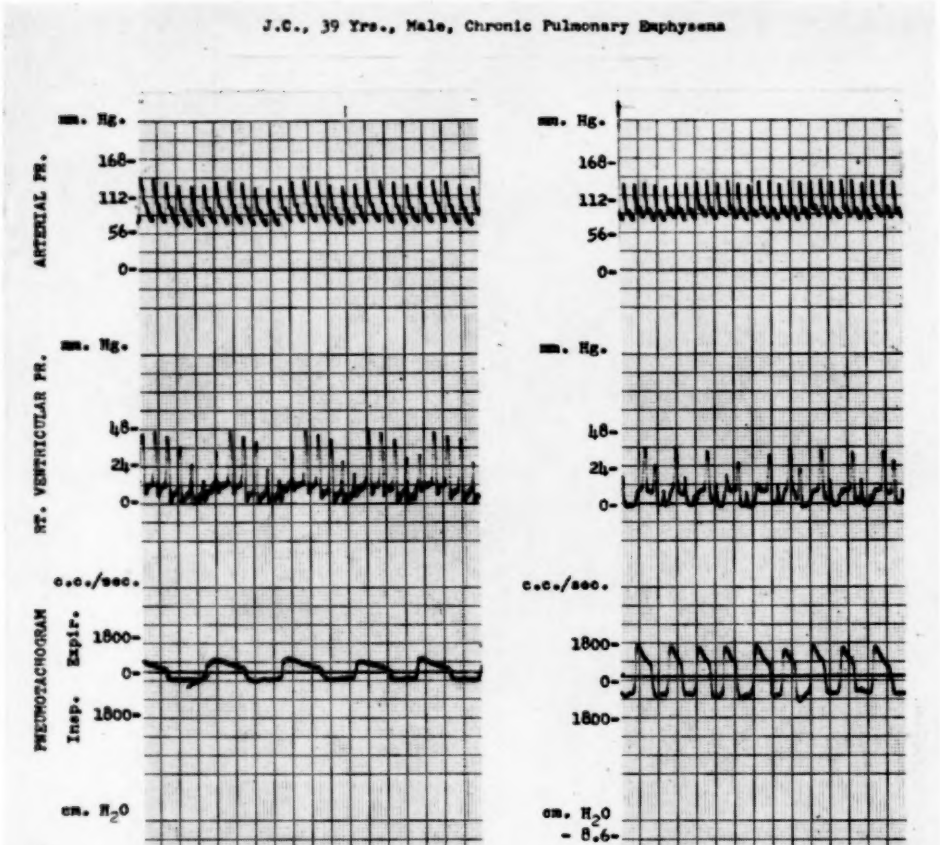

FIG. 3. Ventilatory and circulatory dynamics in a patient with chronic pulmonary emphysema before and after 0.5 Gm. of aminophyllin intravenously. Note that there was essentially no change in arterial pressure, but a reduction in right ventricular pressure and improvement in inspiratory and expiratory airflow rates without any corresponding increase in intrathoracic pressure variation.

ill patients with a large bronchospastic component should be treated in this manner, therapy being continued until all wheezing has subsided; this may take several days. Less severely ill patients may be given aminophyllin rectally, 0.25 to 0.5 Gm. in 15 cc. of tap water every eight hours. The ambulatory patient with chronic cor pulmonale may note increased tolerance for walking and less wheezing while taking an aminophyllin preparation such as Cardalin, which permits higher oral dosage with less tendency toward development of nausea.

Bronchodilator aerosols

Aerosol therapy, consisting of the nebulization of bronchodilator agents, should be employed to relieve bronchospasm (13). The therapeutic agent is

placed in the standard Vaponefrin nebulizer, which is connected by rubber tubing to the regulator of an oxygen tank or an N.C.G.-Eliot air pump, and nebulized with flow rates of 4 to 6 liters per minute (14). When 0.5–1.0 cc. of a bronchodilator (such as Nebu-Prel or 1:200 Isuprel) is used in combination with 1 or 2 cc. of a detergent such as Alevaire, it will help to relieve bronchospasm and to facilitate the raising of mucoid and viscous secretions. We have not noted any tachycardia with the combination of Phenyl-ephrine HCl-Isoproterenol SO_4 (Nebu-Prel). Each aerosol treatment should take fifteen to twenty minutes and may be repeated every six or eight hours for as long as necessary. The use of aerosols with pressure breathing devices will be discussed later.

Phlebotomy

Polycythemia may be manifested clinically by malaise, dizziness, anorexia, plethora and distention of the neck veins. The associated physiologic changes and the differentiation from polycythemia rubra vera have been discussed previously. In the individual patient, it may be difficult to determine the exact point at which the compensatory polycythemia ceases to be beneficial and begins to increase the circulatory load. When the vigorous measures described for relieving hypoxia fail to bring about a reduction in the elevated hematocrit reading, prophylactic phlebotomies should be employed. Since undesirable results may follow the sudden removal of more than 350 cc. of venous blood, it is advisable to withdraw only 250 to 350 cc. at one time, repeating the phlebotomy at intervals of a week or more, depending upon the clinical course. The hematocrit may be used as a guide and should be kept below 50 per cent. Following venesection, the pulmonary arterial hypertension may be reduced. Phlebotomy should be carried out slowly, and before digitalization whenever possible. We have observed more effective digitalization and better clinical results with this procedure. Reduction of the hematocrit from 59 to 43 per cent followed within a week of phlebotomy in one of our patients with chronic pulmonary emphysema and chronic cor pulmonale. This led to an increase in arterial oxygen saturation from 75 to 79 per cent with the patient at rest, and from 57 to 72 per cent during exercise. Simultaneously, the arterial concentration of carbon dioxide (pCO_2) dropped from 69 to 54 mm. Hg.

Oxygen

Certain drugs may be of value in the treatment of chronic cor pulmonale but their use may be dangerous and require caution. These are the sedatives, opiates and high concentrations of oxygen, the dangers of which have already been referred to in connection with the development of respiratory acidosis (2, 15, 16). Oxygen especially may be valuable. The mental state of the patient, rate and depth of respirations, and arterial blood gases may be used as a guide in selecting the concentration of oxygen to be administered. It is best administered at first with a flow rate of 1 liter per minute, by means of a plastic conjoined double nasal cannula. The flow may be increased by small increments (16) over a period of several days until a rate of 6 liters per minute is reached. When this has been

achieved, the N.C.G.-Eliot[1] plastic oxygen face-tent may be employed with flow rates of 6 liters per minute, thus obtaining concentrations of oxygen not exceeding 50 per cent. This method has proved to be more efficacious than intermittent administration. The patient should be inspected frequently at the outset of oxygen therapy for clinical signs of respiratory acidosis. A more effective check is the serial determination of arterial pH and CO_2 tension.

More recently, we have been advising these patients to carry the Oxy-Hale unit—a simple, pocket oxygen device which delivers controlled concentrations of oxygen for inhalation. The reduction in the burdensome problem of ventilation under conditions of exertion has been most striking with the use of this unit. Oxygen concentrations of 40 per cent were delivered to one of our patients whose control arterial oxygen saturation was 57.2 per cent. There was pronounced clinical improvement, associated with disappearance of cynosis and subsidence of orthopnea. Arterial oxygen saturation reached a level of 93 per cent after one minute of therapy involving 18 inhalations. Five minutes after recovery, the arterial oxygen saturation was 69.2 per cent, still above the control value.

Opiates

There is a great temptation to employ opiates to ease the labored breathing of the severely dyspneic patient and give him a few hours of much needed rest. In general, it is best to avoid the use of morphine. When employed, it should be administered with caution. A single small dose of 7.5 mg. may be well tolerated but it should not be repeated. Meperidine (Demerol) has a wider range of safety than morphine and is a more efficacious drug in the treatment of chronic cor pulmonale. Some bronchodilation, mild sedation and atropine-like effects may occasionally be observed. A pleasant state of general relaxation follows its use. Addiction to meperidine, although less frequent than to morphine, does occur and may be of a severe type. Meperidine may be given in a dose not larger than 50 mg. and repeated after an eight-hour interval if indicated. Compared with morphine, there is a somewhat greater range of safety against the danger of respiratory depression. When using opiates and barbiturates, careful watch should be kept for sudden drops in the rate and depth of respiration. The combination of opiates with the sudden administration of oxygen concentrations above 50 per cent may lead to most serious results. One of us (M.S.S.) has observed sudden death in 2 patients with chronic cor pulmonale secondary to severe kyphoscoliosis. Both patients had received repeated doses of morphia and mask-oxygen therapy. The deaths followed the typical pattern of respiratory acidosis, namely, hypoventilation, coma and exitus. In the past, such deaths have been attributed to morphine idiosyncrasy.

Treatment of respiratory acidosis

If respiratory acidosis develops during the inadvertent administration of high concentrations of oxygen, the method should be changed immediately to the

[1] Manufactured by Eliot Medical Plastics, Inc., Lynn, Massachusetts.

nasal catheter technique, with an oxygen flow of 1 liter per minute. If an opiate has been the cause of the respiratory depression, it should be counteracted at once by the administration of N-allyl-normorphine (Nalline)[2]. This drug is pharmacologically related to morphine and has been found in repeated studies (17–19) to be very effective in counteracting the respiratory depressant effect of the opium derivatives and Demerol. Nalline, in a single dose of 2 to 10 mg., should be given intravenously, followed by the administration of another 5 to 10 mg. mixed with 250 cc. of 5 per cent glucose in water by slow intravenous drip.

In the treatment of respiratory acidosis, whether spontaneous or due to the administration of high concentrations of oxygen or opiate (2, 15, 17), it should be remembered that the acidosis is the biochemical response to alveolar hypoventilation. The most important aim in treatment is to improve pulmonary ventilation, for only by so doing can one rid the blood and tissues of the accumulated excess of carbon dioxide and permit the respiratory center to regain normal sensitivity. Any available means of artificial respiration should be used promptly, whether it be with an intermittent positive-pressure breathing unit (such as the Bennett, Dotco or Mark 7 valve apparatus), a Drinker or Emerson type of respirator, or even manual resuscitation as an emergency measure. The intermittent positive-pressure breathing units (IPPB/I) are mechanical devices for giving oxygen or air-oxygen mixtures under pressure during the inspiratory phase of respiration (2, 20). The flow of gas is initiated by an inspiratory effort on the part of the patient and proceeds until the selected pressure is reached. Expiration is entirely passive. Thus, the valve acts as an amplifier for the patient's own inadequate attempts at inspiration. The apparatus may also be operated manually or with a pre-set, automatic cycling device if the patient is apneic. These devices should be used with air, or air-oxygen mixtures, rather than with pure oxygen in the patient with respiratory acidosis. We have demonstrated in the laboratory that expiratory ball-valving may occur in the air-flow velocity tracings of patients with chronic pulmonary emphysema, an abnormality which is not observed after treatment with intermittent positive-pressure breathing. We generally recommend the use of 1 cc. of a bronchodilator aerosol such as Vaponefrin (2.25 per cent) or Isuprel (1:200) with 2 cc. of a detergent such as Alevaire, in conjunction with intermittent positive-pressure breathing. These aerosols increase the effectiveness of ventilation and their administration is easily carried out, since a nebulizer is incorporated in the apparatus for this purpose.

A note of caution should be sounded concerning sustained therapy of this type in patients with cardiac failure and falling blood pressure and in those with inadequate venous gradients for return of blood to the right heart. Because of the increased intrapulmonary pressure during inspiration, both venous return and cardiac output may decrease markedly. In patients with insufficient vasomotor tone, the necessary gradient for maintaining an adequate venous return cannot be re-established and circulatory shock may result. If the mean mask pressure is kept near zero, these untoward effects can largely be avoided.

Manufactured by Merck & Co., Inc., Rahway, New Jersey.

Antimicrobials

A further important aid in the treatment of chronic cor pulmonale is the use of antibiotics. There is often an element of pulmonary infection which may contribute to the severity of the pulmono-cardiac failure and may "trigger" the development of respiratory acidosis (21). If such an infection appears to be present, a suitable antibiotic, determined by bacterial examination of sputum and sensitivity tests, should be given. Most of our patients received parenteral crystalline penicillin, inasmuch as most of the bacterial infections in the lungs of these patients are caused by penicillin-sensitive organisms. One of the broad-spectrum tetracycline antibiotics, such as Achromycin, was employed when exact bacteriologic diagnosis was not made. Chloramphenicol (Chloromycetin) was reserved for patients with predominantly gram-negative organisms, or those who were more seriously ill. Once started, a reasonable program should be adhered to without changes until evidence of infection has been controlled or one's judgment calls for a change or a combination of drugs. The response to antibiotics was usually dramatic in our series. Small daily doses of oral penicillin or Achromycin were administered for prophylaxis of respiratory-tract infections during the winter months, in patients prone to these conditions.

Digitalis

The value of digitalis in the treatment of chronic cor pulmonale has been questioned by some in the past. Digitalis may have little or no effect on cardiac output in the absence of frank right ventricular failure, hence little or no beneficial clinical effects may be observed. Many of the patients observed in this series (Table 2) had evidence of pulmonary hypertension and an increased cardiac output, as manifested by the following: accentuated pulmonic second sound, forceful subxiphoid pulse, full bounding radial pulse, moderate elevation of venous pressure, and warm skin. These patients were digitalized after venesection, bronchodilator therapy, antibiotics and supportive therapy were instituted —in many instances before evidence of frank right-sided failure (hepatomegaly and edema of the legs) appeared. In more recent years, we have given digoxin (Lanoxin) to those of our patients with chronic cor pulmonale who have clinical evidence of either increased or reduced cardiac output with pulmonary hypertension. This precaution may avoid the danger of the serious type of failure with the shortened life-span, to which all these patients are subject. In the treatment of cor pulmonale we prefer to use digoxin for digitalization because of the added safety factors. Its rapid rate of elimination assures shorter duration of toxic manifestations, and it is better tolerated than digitoxin or digitalis leaf in these patients.

In the hospitalized, more seriously ill patients the failure appeared to be of the type associated with low cardiac output, and was characterized by low blood pressure, cold, clammy skin and a weak, thready pulse. Cyanosis of the extremities, oropharyngeal mucosa and conjunctivae, and marked elevation of venous pressure were present in addition to hepatomegaly and edema of the legs. It is reasonable to assume that some degree of left ventricular strain may have been

present in some of these patients in view of the low cardiac output and the possibly inadequate coronary circulation.

The level of cardiac output should be looked upon as the individual response of each patient according to his own metabolic needs. A patient may have different levels of cardiac output in different stages of cardiac decompensation, in line with his attempts to compromise between his metabolic needs and the state of the myocardium. The cardiac output is profoundly influenced by therapy such as oxygen, aminophyllin, diuretics, venesection and restriction of physical activity. Ferrer *et al.* (22) studied a group of patients with cor pulmonale and right-sided failure before and after digitalization with a single intravenous dose of digoxin. The first response was an increase in cardiac output and a reduction in the filling pressure of the right ventricle. Pulmonary artery pressure rose simultaneously, due to increased blood flow into an already diminished pulmonary vascular bed. It should be pointed out, however, that this immediate response was of short duration. As time went on, clinical improvement brought about a decrease in cardiac output, a reduction in the elevated pulmonary artery pressure, and an increase in arterial oxygen saturation. Another group of patients with chronic cor pulmonale, but without right-sided heart failure, showed no changes in cardiac output, right ventricular pressure and pulmonary artery pressure after intravenous digoxin (22).

In our present series of 23 patients, Lanoxin was generally employed for digitalization and maintenance. In 18 patients the initial dosage was 0.25 mg. orally at eight-hour intervals for six doses, followed by a maintenance dosage of 0.25 to 0.50 mg. daily. The other 5 patients were digitalized with whole leaf and subsequently maintained with Lanoxin. The seriously ill, hospitalized patients were digitalized with Lanoxin, employing the more rapid intravenous route.

Control of edema

The course of chronic cor pulmonale and the patient's response to therapeutic agents depends to a large extent on the state of electrolyte and water balance. Salt restriction (low-sodium diet containing 750 mg. of sodium daily) is employed when there is a tendency toward edema formation; it should be rigid enough to keep the patient free of excess fluid accumulation, but no more than that. More generous salt intake may be permitted patients receiving Diuril. Vigorous fluid restriction, on the other hand, is undesirable; an adequate, increased fluid intake aids in sodium excretion. Furthermore, it is essential to maintain a good fluid intake during diuresis in order to avoid dehydration in polycythemic patients who are particularly prone to thrombo-embolic accidents. Careful examination of the liver, search for pitting edema of the sacrum and legs, and measurement of the patient's "dry weight" daily before breakfast were used as guides for evidence of retention of fluids. Rales at the lung bases were evident in only the few patients with combined left and right heart failure and bronchopulmonary infections; at times it was difficult to differentiate the two. Rales were not present in the other patients in this series.

Dietary control, restriction of salt, and digitalization were often inadequate in

controlling edema. The patients had received diuretics at one time or another, in the form of ammonium chloride, oral mercurials, parenteral mercurials, Diamox, Mictine or Rolicton, prior to our employing chlorothiazide (Diuril).

Particular attention should be paid to the low-salt syndrome which may follow too rapid or repeated diuresis. It is characterized by weakness, anorexia, drowsiness and leg cramps. In mild cases, a temporary increase in dietary salt will correct the dietary depletion; in more severe cases, a slow intravenous infusion of 250 cc. of a 5 per cent solution of sodium chloride for one to two days is needed. A compensatory metabolic alkalosis associated with respiratory acidosis, characterized by an elevated level of plasma bicarbonate with a low level of serum chloride, should not be confused with depletion hyponatremia and treated as such. Loss of potassium (hypokaliemia) during rapid or repeated diuresis may be more serious. It may be followed by manifestations of digitalis toxicity and cardiac arrhythmias.

Frequent determinations of serum electrolyte and carbon dioxide levels, hematocrit readings, and electrocardiograms should be obtained in patients undergoing a vigorous therapeutic regimen. It is our custom to recommend 8 to 12 ounces of orange or cranberry juice daily during long-term diuretic therapy. This is supplemented with oral potassium chloride (4 to 8 Gm. daily) when there is evidence of hypokaliemia. When employing vigorous mercurial therapy, or during long-term steroid therapy, we have found Pot-Amide[3] (ammonium and potassium chloride combined) very helpful as a mild diuretic and replacer of lost potassium and chloride.

Chlorothiazide (Diuril) therapy

During a study of aromatic sulfonamides at the Merck laboratories, Novello and Sprague observed especially effective diuresis with benzendisulfonamides (23). Further study revealed another interesting compound, 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, (chlorothiazide), known as Diuril[4] in the United States and Canada and as Saluric, Clotride or Chlotride in other countries.

Chlorothiazide was found to meet the criteria for a better diuretic agent, with respect to inhibition of renal reabsorption of sodium, oral effectiveness, druation of action following single and repeated doses, pronounced excretion of electrolytes in the least harmful way, effectiveness when administered for prolonged periods, proper distribution in the body, minimal physiologic and pharmacodynamic side-effects, high therapeutic index and low toxicity. Extensive studies and clinical trials were carried out with this compound during the past year (24–28).

Chlorothiazide was found to be an effective inhibitor of carbonic anhydrase *in vitro*; however, this was not thought to be the primary diuretic mechanism in humans. Effective oral doses caused marked inhibition of renal tubular reabsorption of water and electrolytes, preponderantly sodium and chloride, and to a lesser degree, potassium and bicarbonate. There were no significant changes in glomerular filtration rate or renal plasma flow. Oral therapeutic doses caused

[3] Manufactured by Angier Chemical Company, Boston, Massachusetts.

[4] Manufactured by Merck Sharpe & Dohme, Inc., Philadelphia, Pennsylvania.

little change in urinary pH but large doses resulted in alkalinization due to increased bicarbonate excretion. Acidosis and resistance did not develop with continued administration. Therapeutic oral doses caused no significant depletion of electrolytes during long-term therapy. Oral administration of potassium was advised in addition for patients with edema caused by administration of steroids and for some patients with chronic congestive heart failure. Chlorothiazide was found to potentiate the effect of antihypertensive agents, permitting a reduction in the dose required for therapeutic effect; the mechanism is unknown (29).

The hypotensive and diuretic effects of chlorothiazide suggested its possible usefulness in the treatment of chronic cor pulmonale. The drug (Diuril) was given to 23 patients with clinically well established manifestations of the disease (Table 2). There were 14 males and 9 females, ranging in age from 47 through 80 years. The chronic cor pulmonale was secondary to severe chronic bronchitis and obstructive pulmonary emphysema in 18 patients, to chronic pulmonary fibrosis in 3, and to severe kyphoscoliosis in 1. Two patients had congestive heart failure secondary to both left and right ventricular failure, 8 had varying degrees of hypertension, and 3 had severe carbon dioxide retention with respiratory acidosis.

In this group of 23 patients, 5 were critically ill, necessitating hospitalization. Prior to starting Diuril therapy, all had been digitalized and were taking some type of oral diuretic; 9 required mercurial injections every one to four weeks; 8 with hypertension were taking Rauwiloid or Rauwiloid-Veriloid; 21 were taking aminophyllin; 20 were occasionally using Vaponefrin bronchodilator aerosol; and 7 were receiving continuous steroid (Hydeltra) therapy.

When Diuril was started, all antihypertensive and diuretic drugs were omitted. Bronchodilator aerosol therapy was permitted only for the control of severe bronchospastic crises. Dietary salt was increased to 1 to 2 Gm. per day, to be divided between cooking and supplementary use in most of the cases. Supplemental potassium in the form of 8 to 12 ounces of orange or cranberry juice daily was urged. Particular attention was paid to changes in the daily morning weights, blood pressure, and clinical manifestations. Clinical evidence of rapid sodium and potassium loss was looked for, and the patients were instructed to report anorexia, nausea, vomiting, weakness, abdominal or leg cramps, visual disturbances and skin rashes. They were particularly requested to note any improvement in shortness of breath, frequency of attacks of bronchospasm, moon-like facies (steroid patients), and edema of the legs.

Vigorous Diuril therapy, employing dosages of 500 mg. four times daily, was attempted in the first 4 patients treated. Because of gastro-intestinal upsets and weakness, this dosage was reduced to 500 mg. three times daily (administered with each meal) in the next 6 cases. It soon became apparent that after three to seven days most of the patients did well with smaller amounts. Ultimately, the dosage was reduced to 500 mg. with breakfast and lunch or with breakfast alone, depending upon the diuretic needs. Several patients with hypertension, and others previously requiring weekly mercurial injections, have obtained continuous benefit from 250 to 500 mg. of Diuril one to three times daily.

An exact estimate of each patient's needs should be made at the time the other

diuretics, steroids and drugs are reduced or omitted. Diuril dosage will vary from time to time, inasmuch as many stress factors, variations in excretion of water and electrolytes, bronchoconstriction, and complicating bronchopulmonary infections are involved in the production of further right-sided heart strain and possible left ventricular heart strain.

During the first month of Diuril therapy, there was a weight loss of 3 to 15 pounds in 15 patients; no weight loss was observed in the other 8. A reduction in edema of the legs and facial mooning was noted in 3 of the 7 patients who were receiving long-term steroid therapy. A significant drop in blood pressure was observed in all 8 patients with hypertension. Fourteen patients reported less shortness of breath, and 1 noted rapid disappearance of paroxysmal nocturnal dyspnea.

Omission of other oral diuretic agents was possible in the 22 patients who had been taking them before starting Diuril. (One patient had not received any other diuretic previously.) In 9 of this group of 22, there was no further need for the injections of mercurials that had formerly been required at intervals of one to four weeks. In several patients who were receiving solutions of aminophyllin rectally because of associated severe bronchospastic crises, it appeared that diuresis was potentiated when Diuril was administered half an hour before the aminophyllin. This effect may have been due to an increased glomerular filtration rate.

The effects of Diuril on pulmonary function were studied in 5 patients with chronic pulmonary emphysema and chronic cor pulmonale. The acute effects were evaluated in 2 patients, one and two hours after the intravenous injection of 500 mg. There was an increase in pulmonary compliance to 118 per cent of the control value and a decrease in resistance to airflow to 60 per cent of the control value. Correspondingly, vital capacity and maximal breathing capacity rose slightly. There was a slight rise in the hematocrit. There were no significant changes in the arterial blood gases.

The effects of oral Diuril therapy on pulmonary function were studied at two-week intervals. These data are more difficult to interpret because of the wide variations of pulmonary function during the natural evolution of emphysema. However, pulmonary compliance increased and resistance to airflow decreased regularly. The changes in vital capacity and maximal breathing capacity were also similar to those observed in the acute intravenous study, though less marked. Except in 1 patient in whom the arterial oxygen saturation rose to 112 per cent of the control value, there were no significant changes in arterial blood gases, though the oxygen capacity rose slightly in each instance. The beneficial effects of Diuril upon pulmonary function seemed to be characterized principally by improvement in the mechanics of breathing, with consequent reduction in pulmonary congestion.

SUMMARY

In chronic diffuse pulmonary disorders in which progressive hypoxia, carbon dioxide retention, pulmonary hypertension and increased pulmonary vascular

resistance occur, the combined effects of these factors ultimately lead to serious impairment of the function of the right ventricle. The combined effects of the primary pulmonary disorder and the secondary cardiac disorder are included in the terms pulmonary heart disorder, pulmono-cardiac failure or chronic cor pulmonale.

Therapy was directed towards both pulmonary and cardiac components. The pulmonary disease was best managed with bronchodilator aerosols, aminophyllin, steroids, antimicrobials, venesection, diaphragmatic breathing exercises, emphysema belts and intermittent positive-pressure therapy. Cardiac failure in cases of chronic cor pulmonale responded best to the effects of oxygen therapy, digitalization with digoxin (Lanoxin) and diuretics *after* the associated pulmonary disease had been vigorously treated.

The use of a new diuretic drug, chlorothiazide (Diuril), was particularly effective in the overall management of the present series of 23 patients with severe chronic cor pulmonale.

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CLINICAL STUDY WITH A NEW HYDROCHOLERETIC DRUG AND A NEW HYDROCHOLERETIC-ANTISPASMODIC COMBINATION

EDWARD SETTEL, M.D.*

Brooklyn, N. Y.

Biliary-tract disorders today are common clinical occurrences, and they can be expected to become even more common in the near future. As Rizzo (1) points out, life expectancy is increasing, and the incidence of biliary disease increases with each decade of life. For this reason, attention has turned toward the more effective management of these disorders.

Current medical management often includes the administration of 1) a hydrocholeretic to effect an increased flow of a clear, fluid bile; and 2) antispasmodic medication to reduce hypertonicity of the sphincter of Oddi and relieve the associated smooth muscle spasm.

This report evaluates the clinical effectiveness of florantyrone (Zanchol®)[1], a new abstergent-hydrocholeretic, and a combination[2] (tablet) of this drug and the antispasmodic agent, Pro-Banthīne®, in the treatment of various biliary disorders. Zanchol is a single, synthetic substance chemically described as γ-oxo-γ-(8-fluoranthene) butyric acid. Pro-Banthīne is a single, synthetic substance with the descriptive formula β-diisopropylaminoethyl xanthene-9-carboxylate methobromide.

Extensive pharmacologic studies (2) on animals indicate that florantyrone is virtually nontoxic. Clinically, Barowsky (3) observed no side-effects in any of 25 patients receiving the drug, even though it was administered over long periods of time. In a study of 156 patients, Schwartz and his co-workers (4) noted only mild, occasional side-effects from the prolonged administration of Pro-Banthīne; these side-effects (dryness of the mouth, blurring of vision and hesitancy of urination) seldom interfered with continuous administration and were reduced notably with adjustment of the dosage.

METHOD

The 36 patients in the present study were divided into 4 diagnostic groups: 19 patients with chronic cholecystitis and cholangitis, 9 with biliary dyskinesia, 5 with the post-cholecystectomy syndrome, and 3 with biliary constipation. They were further divided into a middle-aged group (20 patients aged 35–60 years) and a geriatric group (16 patients aged 61–86 years).

Biliary-tract disease had been present, with or without associated hepatic dysfunction, for periods ranging from three months to twenty-five years. Roentgenologic evidence of biliary-tract disease was present in more than two-thirds of the 36 patients.

Florantyrone was administered as 250-mg. tablets of Zanchol in a dosage of 1 tablet three or four times daily. This dosage was doubled when a greater response was desired. When

* Address: 349 Eastern Parkway, Brooklyn 16, N. Y.

[1] Trademark of G. D. Searle & Co.

[2] Prozanchol (Searle).

pain or spasm in the upper gastro-intestinal tract was reported, associated either directly or indirectly with the primary disorder, a combination tablet of Pro-Banthīne-Zanchol was utilized.

The effectiveness of Zanchol in these patients was assessed by observing the color and quantity of the stool, the frequency of bowel movements, the amount of epigastric discomfort (fullness, eructation, nausea, vomiting) and the subjective feeling of improvement. Two of the patients with the postcholecystectomy syndrome were observed while undergoing T-tube drainage of the common duct, as they afforded visual observation of the bile during the course of treatment.

RESULTS

Results were considered "good" 1) in patients without T-tubes when the stools were dark brown and normal in consistency and frequency, 2) in patients with T-tubes, when the bile became green, fluid and free of sediment, and 3) when symptoms of biliary dysfunction subsided. The findings could be summarized as follows:

	Good Results		Poor Results	
	Middle-aged group	Geriatric group	Middle-aged group	Geriatric group
Chronic cholecystitis, cholangitis	7	6	0	6
Biliary dyskinesia	4	2	2	1
Postcholecystectomy syndrome	4	0	1	0
Biliary constipation	2	0	0	1
Totals	17	8	3	8

It may be seen that in 25 of 36 patients (69 per cent) there was a good response to Zanchol and Pro-Banthīne-Zanchol therapy.

All 6 patients with chronic cholecystitis and cholangitis showing a "poor" response were over 60 years of age; the diarrhea which developed in 4 of them was controlled within five to twenty days. The 2 remaining patients who responded poorly complained of nausea and discontinued the medication. The addition of Pro-Banthīne did not relieve the nausea.

Of the 3 patients with biliary dyskinesia who failed to respond satisfactorily, 1 had diarrhea, and 2 (1 of whom was in the geriatric group) experienced no alleviation of symptoms.

The bile from the 2 patients with the postcholecystectomy syndrome undergoing T-tube drainage became clear and deep green, and contained little or no sediment during Zanchol therapy. The Pro-Banthīne-Zanchol combination seemed to relieve fullness, pain, nausea and vomiting more effectively than did Zanchol alone. The greater relief obtained from the combination was thought to be associated with the antispasmodic action of Pro-Banthīne. This action reduces excessive neural impulses and thus inhibits smooth muscle spasm, gastric secretion, and gastro-intestinal hypermotility.

DISCUSSION

Of the 11 patients showing a poor response to florantyrone (Zanchol) therapy, 8 were in the geriatric group. Good results were observed in 50 per cent of the

geriatric group and in 85 per cent of the middle-aged group. These findings indicate that Zanchol is a highly effective hydrocholeretic in patients up to 60 years of age.

Zanchol enhanced the flow of a clear, sediment-free, fluid bile, and increased hepatic efficiency. The combined Pro-Banthine-Zanchol preparation had an added antispasmodic effect which usually relieved persistent symptoms of fullness, pain, belching and nausea.

Many patients who responded well to Zanchol stated spontaneously that they received greater relief than from any choleretic taken previously. The stools became dark brown, formed, and of normal consistency. Bowel movements occurred at regular intervals (once or twice daily). Appetite improved, and epigastric distress did not reappear.

Zanchol therapy was continued for three or four months in the patients who experienced a good result. There were no side-effects and no detectable evidence of toxicity in the individual hemograms, urinalyses and tests of renal and hepatic function.

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ENHANCED ABSORPTION OF IRON WITH USE OF A NEW HEMATINIC AGENT

(Preliminary Studies)

DONALD C. AUSMAN, M.D.

Milwaukee, Wisconsin

Iron deficiency anemia is a common disorder of the blood. If patients can tolerate large doses of iron, an efficient, economical and practical method of therapy is the administration of ferrous salts by mouth. Ferrous sulfate, however, in adequate doses, is poorly tolerated in about a third of the patients treated, as reported in several studies (1–3). Even the recently developed preparations, such as ferrous calcium citrate with added tricalcium citrate, produce side-effects (nausea, dizziness, diarrhea and constipation) in about 20 per cent of patients (4). Thus there is still a need for an iron preparation that is well absorbed, well tolerated, and highly effective in virtually all instances. Such a product appears to have been developed by taking advantage of the effect of polyol monolaurate on the absorption of iron.

Wissler and associates (5) reported that the prior oral intake of polyoxethylene sorbitan monolaurate greatly increased the gastro-intestinal absorption of radio-iron (Fe^{59}) in the golden hamster. Although the study was designed to demonstrate the safety of the polyol monolaurate even when administered for prolonged periods, the data also indicated that the compound had an effect upon the absorption of iron. It was found that the amount of iron present in the gastro-intestinal mucosa, bone marrow, and blood was more than twice as great three days after the combined administration of Fe^{59} and polyol monolaurate than when Fe^{59} was administered alone.

The acute lethal dose (LD_{50}) of polyol monolaurate in mice was reported by Hopper, Hulpieu and Cole (6) as 3.75 Gm. per Kg. intravenously in twenty-four hours and 25.0 Gm. per Kg. orally in seventy-two hours.

Numerous reports of studies made on the acute and chronic toxicity of polyol monolaurate in various animal species have appeared in the literature. They are generally in agreement that the compound is almost without demonstrable toxicity when administered orally, except when the amounts are such that there is interference with normal consumption of food. Polyol monolaurate is well tolerated when administered parenterally, even in concentrations up to 5 per cent.

Extensive feeding studies in the laboratory of Krantz and associates (7) showed polyol monolaurate to be innocuous in concentrations of 0.5 to 2.0 per cent in the diet of the white rat for nearly the life span. Also, the feeding of 1.0 Gm. of polyol monolaurate daily to the Macacus rhesus monkey (4 animals, seventeen months) produced no significant histologic visceral changes.

The capsule which makes possible the administration of physiologic rather than excessive doses of iron to produce a relatively constant hematinic response

has been designated as "Simron."[1] Each soft gelatin capsule contains ferrous gluconate equivalent to 10 mg. of elemental iron plus 400 mg. of polyol monolaurate (Sacagen)[2] The first preliminary observations were conducted in patients with iron deficiency anemia who were given daily doses varying from 1 to 8 capsules. The first patient to whom Simron was administered in a dosage of just 1 capsule daily (equivalent to only 10 mg. of elemental iron) exhibited such a surprising response that she was not tested with the dose later proposed as adequate. During a period of nineteen days her blood hemoglobin level rose from 9.95 Gm. per 100 cc. to 12.45 Gm. The actual increase in the circulating iron incorporated in red cells was greater than the total dose of 190 mg. of iron in the 19 capsules of Simron taken during the test period. Apparently the Sacagen enhanced the absorption of dietary iron, as well as of the ferrous gluconate in the capsule.

Final selection of a dosage of 1 capsule three times daily resulted, at least in part, from the experience with a second patient (No. 24 in Table 1). In the four-week test period during which Simron was given in a dosage of 3 capsules daily, the hemoglobin level rose from 11.8 Gm. per 100 cc. to 12.2 Gm. The dosage was then reduced to 2 capsules daily, and during the next four weeks the hemoglobin level fell to 11.4 Gm. per 100 cc. The dosage of 3 capsules daily was restored, and during the next four weeks the concentration of hemoglobin rose to 11.8 Gm. per 100 cc.

METHODS

All hematologic technics were carried out in our own laboratory by 2 experienced technicians. Photoelectric hemoglobin determinations were performed with a Leitz (Rouy) photometer which had been rechecked at the beginning of the study by means of calibration against a known standard iron solution (8).

Because the striking increase in the utilization of iron following oral administration of small physiologic amounts of iron combined with polyol monolaurate was first demonstrated by means of an increase in the hemoglobin level, the present preliminary report is confined to a discussion of changes in hemoglobin. However, all of the patients were also studied with respect to red blood cell count, reticulocyte response, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, and serum iron level. These data, both for patients in the present series and those currently under study, will be reported later.

MATERIAL

All 26 patients studied were white adults; 8 were men and 18 were women. The ages ranged from 20 to 82 years (average, 46.9 years). They were from the middle-income group and all were private patients. Usually the level of hemoglobin was less than 12 Gm. per 100 cc., but in 2 cases which might otherwise have been called "borderline", the diagnosis of anemia was based on the low value for mean corpuscular hemoglobin.

Six of the 26 patients had received other forms of iron previously, so that comparative data on absorption were available.

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[1] Simron is the trademark of The Wm. S. Merrell Company, Cincinnati 15, Ohio, for this capsule.

[2] Sacagen is the trademark of The Wm. S. Merrell Company for its brand of polyoxyethylene glucitan monolaurate.

RESULTS

The percentage of iron which is absorbed and is incorporated into the circulating hemoglobin following oral administration of 1 Simron capsule was calculated, on the assumption that the amount of blood in the average body is approximately 5 liters. On this basis, when Simron was administered in a daily dosage of 3 capsules containing a total of 30 mg. of elemental iron (as ferrous gluconate), 28.8 per cent (average) of the iron in the capsule could be accounted for by the iron in the increased amount of circulating hemoglobin. The values for each of the 26 patients are listed in Table 1. Although the average value for absorption and incorporation of administered iron into hemoglobin was 28.8 per cent, the variation was wide, and ranged from a negative iron balance in 1 case (microcytic anemia of unknown etiology) to an increase of over 100 per cent in 2 cases. Similar calculations by others have revealed as little as 1.3 per cent incorporation into circulating hemoglobin for reduced iron (9) and an average of 2.5 per cent for an iron salt (10).

TABLE 1. *Utilization of Iron in the Form of "Simron" (30 mg./day)*

Patient		Diagnosis	Duration of Therapy (days)	Hemoglobin (Gm./100 cc.)		Iron Utilized (%)
No.	Age & Sex			Initial	Final	
1	59 M	Arthritis	28	11.4	12.45	18.7
2	9 M	Arthritis	4	14.2	15.55	168.3
3	54 F	Arthritis	28	10.6	12.2	28.3
4	66 F	Arthritis	104	10.6	11.8	5.5
5	82 M	Cancer (cecum)	14	7.5	8.35	30.0
6	68 M	Cancer (pancreas)	12	8.0	8.6	25.0
7	57 F	Gallbladder disease	21	11.4	13.1	41.6
8	42 F	Glomerulonephritis	24	9.6	11.4	37.5
9	30 M	Glomerulonephritis	28	10.2	11.8	28.5
10	50 F	Hypochromic anemia	28	11.4	12.45	18.7
11	48 F	Hypochromic anemia	28	12.45	13.4	18.7
12	49 M	Hypoproteinemia	28	12.45	13.8	24.0
13	46 F	Menorrhagia	28	8.6	9.95	24.0
14	48 F	Menorrhagia	28	8.9	9.55	11.5
15	20 F	Menorrhagia	28	9.95	11.4	26.0
16	48 F	Microcytic anemia	28	10.2	9.95	−4.4
17	46 F	Nutritional anemia	28	9.95	12.45	44.5
18	42 F	Nutritional anemia	28	11.4	11.8	7.1
19	44 F	Nutritional anemia	28	10.5	11.4	16.0
20	55 M	Nutritional anemia	28	12.8	13.1	5.5
21	30 F	Nutritional anemia	13	11.4	11.8	15.5
22	48 F	Nutritional anemia	21	11.4	11.8	14.1
23	35 F	Nutritional anemia secondary to ulcerative colitis	7	9.55	11.0	103.5
24	24 F	Nutritional anemia	28	11.8	12.2	7.0
25	24 F	Nutritional anemia	28	11.2	12.2	17.8
26	45 M	Postoperative and postinfectious anemia	84	11.8	14.6	16.7

TABLE 2. *Comparison of Hemoglobin Responses to "Simron" versus Other Iron Preparations*

Patient	Diagnosis	Iron Preparation	Daily Dose of Iron (mg.)	Duration of Therapy (days)	Hemoglobin					Iron Rise per Day (mg.)	Iron Utilized (%)
					Blood level (Gm./100 cc.)		Rise per day	Rise per 5000 cc.			
					Initial	Final					
M. A.	Nutritional anemia	Simron (1st course)	10	19	9.95	12.45	0.132	6.60		19.8	198.0
		Simron (2nd course)	10	56	11.0	11.8	0.014	0.70		2.1	21.0
		Ferrous sulfate & cobalt preparation	120	26	11.4	13.1	0.0655	3.275		9.83	8.2
S. D.	Arthritis	Simron	30	104	10.6	11.8	0.011	0.55		1.65	5.5
		Ferrous sulfate	240	25	10.6	11.8	0.048	2.4		7.2	3.0
H. H.	Rheumatoid arthritis	Simron	30	28	11.4	12.45	0.0375	1.875		5.63	18.7
		Ferroglycine sulfate complex	120	91	12.2	11.4	decrease	decrease			(drop)
E. M.	Nutritional anemia	Simron	30	28	10.5	11.4	0.032	1.60		4.80	16.0
		Ferroglycine sulfate complex	120	30	7.8	12.2	0.113	5.65		16.95	14.1
P. R.	Terminal cancer of the pancreas	Simron	30	12	8.0	8.6	0.05	2.5		7.5	25
		Ferrous sulfate & cobalt preparation	160	53	8.6	11.8	0.060	3.0		9.0	5.6
C. T.	Menorrhagia	Simron	30	28	9.95	11.4	0.052	2.60		7.8	26.0
		Ferroglycine sulfate complex	120	84	9.55	11.0	0.018	0.90		2.7	2.3

Six of the 26 patients had received other types of oral iron therapy in the past. The comparative responses are outlined in Table 2. The patient with arthritis (S.D.) whose increased hemoglobin level during Simron therapy accounted for only 5.5 per cent of administered iron had previously received ferrous sulfate in dosage of 240 mg. of elemental iron daily; only 3.0 per cent of the iron from that preparation could be accounted for later by increased circulating hemoglobin. The patient with cancer of the pancreas (P.R.) had previously received a ferrous sulfate and cobalt preparation in a dosage equivalent to 160 mg. of iron daily; the amount of iron from this preparation that was incorporated into hemoglobin was 5.6 per cent compared with 25.0 per cent for Simron. Three of the 6 patients had been treated previously with a ferroglycine sulfate complex. It is noteworthy that 1 of them (H.H.) exhibited a decline in hemoglobin level during treatment with ferroglycine sulfate complex and that the best response to that preparation in the other 2 was 14.1 per cent. During Simron therapy, however, utilization was more than doubled in 1 case (presumably because dietary iron was absorbed better in the presence of Simron); and in all cases the response was better to Simron than to the ferroglycine sulfate complex.

Of particular interest was the freedom from side-effects during administration of Simron. There was hardly enough unabsorbed iron left in the gastro-intestinal tract to color the stool. One of the patients with glomerulonephritis and an elevated blood urea nitrogen level complained of some nausea and occasional emesis after he had been taking 3 capsules of Simron daily for about ten days. He continued to take the medication in the prescribed dosage, and after two weeks the symptoms disappeared. Simron has been given for over four weeks since that time without any recurrence of symptoms. None of the other patients in this series complained of nausea, vomiting, diarrhea, constipation, or abdominal distress of any kind. It would appear that Simron permits the doctor to administer a physiologic dose of iron rather than a gross overdose, with assurance that absorption will be sufficient to correct the iron deficiency state without leaving an excess of iron in the gastro-intestinal tract to produce irritation.

In order to ascertain whether excess iron accumulated in the body following correction of the anemia, serum iron determinations (Trinder method) were made in some of the cases after the blood findings had returned to normal, and also after the continued administration of Simron for the purpose of building up iron storage depots. All serum iron determinations were within normal limits, indicating that even during prolonged administration of the drug, overdosage would not be a potential hazard.

SUMMARY AND CONCLUSIONS

A preliminary report has been presented on the absorption of iron following oral administration of a new capsule preparation of ferrous gluconate and polyol monolaurate (Simron). The suggested dosage is 1 capsule three times daily, containing the equivalent of 30 mg. of elemental iron per day. Because the

absorption and utilization of iron (as calculated from increased circulating hemoglobin after therapy) averaged 28.8 per cent, it was seldom necessary to give more than 30 mg. of iron daily. Such a physiologic dose of iron, almost 30 per cent of which was absorbed, produced transient side-effects in only 1 of the 26 patients studied. Absorption and utilization was better with Simron than with ferrous sulfate, a ferroglycine sulfate complex, or a ferrous sulfate and cobalt preparation, in those patients who had received previous courses of iron therapy.

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EMOTIONAL PROBLEMS OF ADULT CANCER PATIENTS

BEATRIX COBB, PH.D.*

Section of Medical Psychology, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas

The emotional problems of the adult cancer patient are complex and severe. A diagnosis of cancer precipitates the patient into a state of biologic defenselessness against danger that is difficult to tolerate. Since there is no simple physiologic explanation of cancer, the psychologic implications are naturally devious and frustrating. A galaxy of realistic threats, then, converge around the diagnosis of cancer. One constellation of anxieties revolves around the unknowns of the disease itself. Another rotates around the stress of enforced dependency in a new and sobering world of the hospital. Still a third configuration has to do with the psychologic strain engendered by the prospects of temporary and permanent separation from the family, with the urgent financial and emotional problems this intervention implies.

The manner in which these real or imagined fears are handled depends upon two factors: the basic personality of the patient and the psychologic skill of the treating physician. As the professional person in this relationship, it is the physician who is responsible for protecting the patient as much as possible from unnecessary fears. One of the most potent weapons in the therapeutic management of the cancer patient seems to be the full knowledge of the psychologic meaning of the disease to the individual. Yet many doctors see only a few cancer patients each year. This gives little foundation upon which to base evaluations of the emotional reactions of their patients to the diagnosis. An analysis of the psychologic reactions of a sample of patients to the diagnosis of cancer might well prove of value to physicians in making this evaluation, and lend further insight into the skill of humanistic management of the emotional factors of cancer. It is the purpose of this paper, therefore, to consider these three major constellations of anxiety as a galaxy of pressures impinging upon the individual in accordance with his own emotional interpretation of the meaning of cancer, as revealed in the psychologic case histories of 40 patients.

THE PSYCHOLOGIC THREAT OF CANCER

Cancer means different things to different people. In accordance with that individual meaning, the patient perceives the threat of the disease. He may have qualified fears for his life, the loss of a body organ or its function, intractable pain and suffering, and chronic invalidism. Strange as it may seem, he may also perceive the diagnosis of cancer as no more dangerous than that of any other illness.

In this study, the intimate meaning of cancer, to 40 patients (13 men and 27 women) was explored. All members of the sample knew they had cancer.

* Head, Medical Psychology Section.

The exploration was carried out through the use of a focused interview designed to elicit emotional reactions to the diagnosis and meaning of the disease, hospitalization, and separation from the family. The patients suffered from a wide range of cancer by site (including the skin, cervix, prostate, thyroid and breast) and melanoma.

Analysis of Threats

An analysis of the threat of cancer as perceived by these 40 patients may be divided roughly into 4 general categories. There seemed to be a continuum of anxiety expressed, running from "no appreciable threat," through a vague unassimilated fear labeled "nonspecific," to a verbalization of "specific" anxieties, to terminate in a small group who seemed to maintain an intelligent "controlled fear" status (Table 1).

1. *No appreciable threat*

Strange as it may seem, 5 of the 40 patients (12.5 per cent) reported no undue stress arising from the diagnosis of cancer. This absence of conscious anxiety was explained by the patients as follows:

"It was just a disease to me, and I didn't know what to expect really."

"I didn't see how it could be serious; it didn't hurt me none."

"I thought it was just one of them little old tumors."

"I didn't know the meaning of 'melanoma' when they told me I had it."

"I was not mature enough to understand what it meant."

The first 3 explanations stemmed from a real ignorance of the disease, and came from patients who had no record of prior experience with cancer. They had little education, and their style of life precluded their having been reached by cancer education literature, which seems to be "geared" to the middle class rather than the lower class population.

The fourth reason for having no fear of the diagnosis of cancer was given by a college graduate, a young man in his first year's internship in oil engineering. His mother had noticed an enlarged node in his neck while he was visiting her in an Eastern City, and had insisted that he go to a doctor. He did so, thinking that the node was a swollen gland. The doctor who performed the biopsy went on vacation before the report came back. The doctor to whom he had entrusted his patient told the patient he had melanoma, and that his doctor would probable wish him to undergo surgery. Whereupon several other doctors who were on rounds joined with the second physician in explaining the situation to the patient, and started discussing the effectiveness of surgery versus radiotherapy. The final conclusion was that they would await the return of the doctor whom the patient first visited. The discussion with the patient meant merely that the doctors could not agree as to whether or not he needed surgery. None of the seriousness of the disease was communicated. Since the patient was overdue to report back to work in the Western portion of the State, he took his de-

TABLE 1. *Threat of Cancer as Expressed by Adult Patients*

Threat	No. of Patients	Per Cent
Not appreciable	5	12.5
Nonspecific	10	25
Specific	21	52.5
Controlled	4	10
Total	*40*	*100*

parture. It was not until a year later, when the node had grown greatly and his general health seemed lower than usual, that the young man again presented himself to the doctor. At that time he had widely disseminated melanoma, did not respond to chemotherapy, and died six months later. Melanoma is such a vicious type of cancer that the life of the patient could not have been insured by early treatment, but there are many melanoma patients who have survived more than seven years following prompt and definitive therapy.

The fifth patient in this category stated that she was not mature enough at the time of diagnosis to understand all the ramifications of the disease. She was a woman in her thirties who presented herself to the physician because of aperiodic vaginal bleeding. She had delayed until drastic surgery plus irradiation was not sufficient to save her life.

2. *Nonspecific threat*

That 10 (or 25 per cent) of the 40 patients reported vague fears focused around cancer indicates the importance of the physician's understanding of the etiology and manifestations of "fright neurosis" in such instances. Alerted to these symptoms, he will not be misled by the patient's apparent lack of anxiety or inability to verbalize fears, nor will he be deceived by the one who is too cheerful. The 10 patients reporting vague, unassimilated fears upon learning they had cancer did not verbalize a fear of death per se, although it was strongly suggested as potently present. One patient was unable to express his feelings other than to say, "It just seemed like one of those things that you think can't happen to you." Another said, "I had mixed emotions about it," but he was unable to verbalize those emotions even when pressed. Four simply said, "I was scared to death." One gave a description of acute psychologic shock as a reaction to being told she had cancer:

"I guess I was just petrified when he (the doctor) told me. I came through the operation in a stage of what seemed like exaltation, or joy, and felt completely unafraid. I seemed at peace with the world, but didn't seem attached to it. I made up poetry all the time, and fell back on religion. I was living in a world above earthly woes. . . . Then, it wore off and I came back to earth with a bang. Now, I realize that I was simply in a daze. I was so petrified, I didn't know what was happening to me really."

This patient had cancer of the thyroid, which can usually be controlled with adequate surgery, but the diagnosis of cancer had produced a shock so great

that the doctor's explanations simply did not penetrate. She accepted the diagnosis as the assurance of death, prepared for her departure, and renounced the world. When it became apparent she was going to live, she had to have psychologic help in accepting life and the duties it demanded.

3. *Specific threat*

More than half the 40 patients (52.5 per cent) reported specific personal meanings that cancer held for them. Twelve persons verbalized death as synonymous with the term "cancer." A man in his late fifties expressed the consensus:

"If you got it, it ain't no use to run to a doctor, for he can't do nothing for you anyway. . . . you're gonna die. I seen my old daddy die of the same thing, just like I got. I know."

Because this patient was so sure that cancer meant death, he did not appear for treatment for a whole year after the first symptoms. He did die of cancer of the stomach just as his "old daddy" had, thirty years before.

A young girl, whose husband and mother found it difficult to tell her the diagnosis, relates her anxiety when she learned she had cancer:

"I was having difficulty breathing because of my over-sized thyroid gland, I guess; so I was propped up in bed. It just happened that day that there was an article about this hospital in the local paper, telling about the new building and what it was for and what it did. None of my family, I guess you would call it, had the nerve to tell me what was really wrong, . . . well, not the nerve, but they just didn't know how to tell me. You can understand that. I mean they didn't know just how to say it or how to explain it to me, because cancer, I believe, to everyone in the outside world is a word that actually means death to you if you don't get it in time, and I think that is the way you would find most people feel about it. Well, as I was saying, this article did come out and my husband brought the paper in and laid it on the bed and asked if I had read the paper that day, and I said, 'No'; and so he just left it laying there and after I finished the story I was reading, I picked it up to read it. There in this very bold print was the hospital story on cancer. Well, it dawned on me immediately what I had, and I dropped the paper. . . I guess you would say, like it was on fire, and I laid it down, and for a minute I was stunned. I just couldn't believe it could be happening to me, because I am not old and decrepit; I thought I was too young for something like that to happen. Then I started crying. I guess, as any woman would, when things go wrong we start bawling. Then I started asking questions, 'Where is it?', 'How far has it gone?', and 'What will they do for me?' My family couldn't answer these questions, and there was about a week or two that I must lay there and all kind of imaginations ran through my mind. But all the time, though I tried to hope, I felt like I was going to die.',

A young man of 19, bright and curious, inadvertently learned he had cancer when his insurance papers were returned for signature, following early hospitalization for lymphoma. When he saw the diagnosis in the papers, he went to a medical dictionary to find out what he had. The dictionary explained that the disease was usually fatal, with a prognosis of approximately five years. The patient describes his reaction:

"I was in the house alone that afternoon. I read it and the shock was so great that it just didn't soak in for a moment. Then I read it again, and tried to jump up, but I guess I blacked out. Anyway, when I 'came to' I was running as hard as I could down the street

several blocks from home. I'd think of something, and something would say, 'That's gone.' I'd black out again for a bit, and then something else would come to me, and again something would say 'That's all gone.' I kept going without really knowing where I was going, but unconsciously I guess, I was going toward the hospital, for after a while I realized that I wanted to talk with the doctor. It's a good thing the hospital was in the same town I was and not too far away. I didn't stop, as far as I can tell, until I got to the hospital and demanded to see the doctor. He took one look at me and sat me down and we talked for about an hour about it. It was bad to find out about it that way; it was just like walking up to a sleeping man, shaking him hard and saying to him, 'You're gonna die right now!' "

The threat of cancer occasionally triggers a psychotic episode in patients of unstable backgrounds. Although these episodes seldom occur, the doctor should always be alerted to the possibility. This is illustrated by the case of a Czechoslovakian spinster in the study series. She had witnessed the death of a sister from cancer of the breast. The patient had cancer of the thyroid, which could have been controlled. She became uncooperative and was referred to the psychologist. She explained her behavior:

"I want to go home. I no can get well. I have chickens and a cow at my house. I have flowers. . . they are so pretty (voice breaks, tears threaten, then she sits up suddenly rigid and claws violently at the lump in her throat). I have cancer. I have cancer here. I die. I die. I know, I die."

This conviction persisted despite efforts to reassure her, on the part of the psychologist and the physician. The patient withdrew from the hospital. Several days later her family physician reported that she had been hospitalized in a mental institution.

To 4 other persons in the sample, cancer meant specifically a punishment for prior transgressions, or a social stigma. A 68-year-old man explained, "I ain't no good. I've been wicked all my life. I had it coming to me." A colored woman was convinced that God had sent cancer of the breast upon her because she sold beer at her "eating place." She had sent for a "prayer cloth" through the mail and waited nine weary and painful months, while the tumor in her breast fulminated and broke into a running sore, hoping that God would forgive and heal her. To some patients, having cancer was experienced as a social stigma. One stated quietly, "It's a disgrace to have cancer." Another elaborated on this theme:

"I know people look at you real funny when you say you are coming here for treatment. . . like I have two heads or something. . . or maybe leprosy and was unclean. I just don't mention to people I have cancer any more."

Of interest also were several specific visualizations or fantasies concerning cancer, reported by the patients whose basic fear was death. One woman with melanoma described cancer as a "huge, black tarantula-like thing pushing its black tenacles inside your body until it takes over and you die." The emotional manner of reporting this fantasy indicated that the patient was living with a very real visualization of an octopus-like viciousness within her, literally taking over her life and pushing her toward sure death. Still another reported:

"I could just see something about this big (approximately 4-inch) oval with little seaweed-like things growing off it. I would just see them wiggling and floating around.

(Shudders at the memory.) It looked real clammy and horrible to me. It was awful to think about it being in your throat. I'd nearly choke to death, just thinking about it."

4. *Controlled threat*

Of the 40 patients studied, only 4 really worked through the threat of cancer intelligently and arrived at some controlled acceptance of the disease and its probable consequences. Knowledge of the course of cancer and the scientific advances toward its control seemed to be the determining factor that made possible this acceptance. The patients speak:

"I was absolutely petrified when this friend told me I had cancer, but I had the good sense to call my doctor, and after I had talked to him, I felt so much better. He was blunt, but he gave me courage and hope. He said, '——, you have met hard problems before and this is just another one. You are an adult, and I know you would want to know. I want you to put your house in order before you go down there for treatment. . . I mean your spiritual house as well as your mental and physical house, and then go down there and give those doctors everything you have in you to help them get you well. You know the doctor can do only so much, and then it's up to you.' I appreciated that so much in the days to come. I talked with other doctors, I read, and I found out what my chances were, what they had to offer in the way of treatment, and then I set myself to help the doctors help me."

This patient had cancer of the stomach. She is alive and doing well six years after this episode.

The other 3 of the 4 patients verbalized less eloquently, but had much the same experience:

"I have read all about cancer. I know my chances for control. I know it is a hard fight for it."

"I know about malignancies. My wife had one too. You face such things, get the best possible medical care, and keep it controlled".

"These things happen and you make the best of them, well aware of your prognosis and the treatment available."

To be told you have cancer, then, may mean different things to different persons. This meaning may range from "no appreciable threat" through "nonspecific fear" and "specific fear" to "controlled fear." The location of each patient's reaction along this continuum indicates the axis of his anxieties.

Revolving around this axis are further psychologic problems connected with the psychologic meaning of the body organ or function involved, the presence or absence of obnoxious odors, deformity from radical treatment, severity of pain, and many other lesser satellites of the basic fear of the disease itself.

The Psychologic Meaning of the Organ Involved

The psychologic meaning of the body organ involved often becomes the crux of trauma for the patient. For example, to the female, so symbolic has the breast become in sexual attractiveness that one young unmarried girl suffered a serious mental depression following radical mastectomy. She verbalized her fears in terms of loss of the right to marriage because of the loss of her breast. Although the use of prosthesis made the loss almost unnoticeable to the casual observer,

this girl felt that the love of a young husband would be turned to repulsion when the scars of the missing breast were revealed. Married women, long past the honeymoon stage, have also voiced these fears. The loss of a breast, to a woman, is a strong threat to her sexual attractiveness and her right to love and be loved. Although many women go through the radical surgery without voicing their true feelings, it is important that the surgeon know the import of this loss to the patient in order to deal with the traumatic feelings.

When a woman has cancer of the cervix, she often feels a violation of womanhood as well. A patient expressed these fears eloquently:

"When I was getting ready to go to the hospital to have radical surgery on my cervix, I was packing my things when my husband came in. We had just been married about six months, he was my second husband, and when he saw that I was packing my wedding gown, he said, 'What are you going to do with this? Make me jealous and give all the interns a treat!' He was just kidding, but to me it wasn't a joke at all. I told him, 'No, but I somehow want to wear this wedding gown tonight because I feel like this will be my last night as a whole woman.' Of course, he scoffed at me, but that is the way I felt. You go in there, knowing that when you come out you can no longer function as a normal woman. It's like taking away your womanhood."

Still another young married woman whose husband placed value on a large family, came back to the ward from her first deep x-ray treatment in a state of hysteria. When the nurse called the psychologist to quiet her, the psychologist explored the emotions precipitating the episode, and found that the patient had overheard the physicians discussing her future sterility just before she was sent to the treatment room. Although she had known before, while isolated in the treatment room she kept brooding on this fact until she had convinced herself that she would no longer be loved by her husband if she were sterile. Along with this fear, she experienced even more drastic anxiety because she had not talked through the treatment with her doctor and she was not sure that she could maintain physical marital relationship with her husband following treatment.

Such emotional reactions are not confined to women. Among the patients studied was a man aged 58, suffering from cancer of the prostate. His wife reported that his emotional reaction to the diagnosis was so much greater than the prognosis seemed to warrant that she was alarmed. He had never verbalized his fears, however, and it was not until he was returning to consciousness following surgery that she realized the focus of his anxiety. Over and over again, as he was returning to consciousness he said how sorry he was that she would be tied to half a man for the rest of his life. To him the prostatic surgery and invasion meant loss of manhood as reflected in adult sexuality. This loss was a greater shock to him than the threat to his life.

Summary of the Psychologic Threat of Cancer

Some definitive knowledge of expected reactions to the emotional impact of cancer would seem of value to the doctor as he conducts the diagnosis-revealing conference with his patient. Medical management may be facilitated and the

trauma ameliorated, if the doctor is alerted to the range of possible interpretative meanings of cancer to the patient.

If no appreciable threat seems to be felt and the patient is accepting treatment, the physician may decide to let the case rest. If the patient is refusing the treatment prescribed because he is oblivious to the seriousness of the diagnosis, the doctor may wish to explain the dangers further.

If the threat of cancer is regarded by the patient as vague and nonspecific, the physician may feel that this reaction is a reflection of "shock neurosis" rather than stolid acceptance of the fact, and wish to proceed on that premise in accordance with the needs and strengths of that particular patient. If the threat is highly specific, the doctor may wish to utilize this preparation period for the purpose of removing erroneous ideas and replacing them with facts concerning cancer. These facts often prove to be a potent antidote to anxieties which mobilize later as the diagnosis "sinks in," when no doctor is present to reassure the patient. Intelligent, controlled anxiety would seem the goal of the preparation period when cancer is diagnosed. This final purpose may not always be accomplished, but with the physician starting where he finds his patient on the compendium and working through the personal meaning of cancer, perhaps this should be the goal. Whatever the final accomplishment, confidence between the patient as a person and the physician as a man is enhanced, and this in turn expedites the flow of communication so essential to the psychologic comfort of the patient. As the doctor listens to his patient and as he responds to the spoken and latent fears, he paves the way for acceptance of the diagnosis and the intelligent participation of the patient in treatment.

THE NEW AND FRIGHTENING HOSPITAL ENVIRONMENT

The constellation of anxieties revolving around the frightening and unaccustomed horizontal world in which the adult cancer patient finds himself are also severe. An enforced dependency role is particularly traumatic to the adult who has obtained and cherished his independence since adolescence. The patients are usually household heads, with all the responsibilities the term implies. To be catapulted suddenly from the role of protector and provider to that of the shielded and provided for, is often an anxiety-producing experience. Uncooperative or irrelevant behavior may reflect the embarrassment suffered by the patient as he lashes out at the more fortunate citizens of the active outside world he so recently left. Such patients are those who recently have faced the sobering experience of fear of illness, and who have approached a physician in unaccustomed humility and suppliance, or in skepticism and doubt, as the case may be. Either way, they find themselves in a position of an uneasy dependency upon strange women nurses and seemingly impersonal doctors. What the doctor and nurse say and do, and the way they say or do it, become fraught with emotional connotations resulting from a combination of the patient's anxiety concerning his disease and adult frustration engendered from forced dependency.

The doctor and the nurse loom as the important figures in the hospital world, and are potentially a source of either emotional comfort or uncertainty for the

adult patient. An atmosphere of warmth and cheer gives the patient courage to fight the disease. The attitudes of the nurse and the doctor assume unprecedented emphasis. The patients do not want sympathy, but yearn for empathy, which preserves their feeling of dignity as important human beings.

Communication becomes of the utmost importance—two-way communication, in which patients not only are talked to, but are listened to as well. They wish to be told "how and why" they are to be treated. When the doctor does not explain in simple words, he engenders new and often unnecessary anxiety. An example of this is a patient who had been told a year before coming for treatment that he should have an immediate operation for prostatic cancer. Because of his ignorance as to how this surgery would be accomplished and the location of the prostate, he refused treatment. When he finally appeared, the disease was in an advanced stage and treatment was of no avail. Unanswered questions are particularly frustrating. One patient said, "If only the doctor would take time to answer the patients' questions. They may sound simple to the doctor, but these simple questions are sometimes the size of an elephant to the patient."

Treatment so familiar to the doctor and nurse as to become routine, may be strange and uncomprehensible to the dependent adult. A routine dose of radioactive iodine almost precipitated a family crisis because the physician had not explained the details of the procedure. A young woman with thyroid cancer was to be given radioactive iodine for a recalcitrant node following surgery. The family members had read newspaper accounts of the effects of atomic energy. When the doctor recommended that on the day following administration of radioactive iodine they limit their visits to the patient to five minutes each, they became distraught. They did not communicate their fears to the doctor, but the patient confided to the psychologist that her mother and husband had visions of her lying abandoned on a bed in a barred room, suffering from lack of food and water, and with atomic energy bursting all around her. They were so alarmed at their imaginings that the patient also became upset. When the doctor sat down and explained the procedure and the precaution of limiting visitors, they cooperated wholeheartedly and all went well.

Summary of Anxieties Related to the Hospital

In the strange world of the hospital the adult cancer patient finds either assurance or disquietude in the emotional climate of the ward set by the nurse and the doctor. The personality of these important inhabitants of his new world, their ability to make him feel their deep interest in him as a person, and their skill in communication, become vital to his courage to face the complex threat to his life and well being.

ANXIETIES REVOLVING AROUND THE FAMILY

The emotional problems of cancer patients in relation to the family constellation are deep and diverse. The problems may have to do with financial security in this time of stress, extending to the future security of the children and marriage partners. Usually, the patients are preoccupied with attempts to

shield family members as much as possible from the ravages of their approaching death. Once in a while, they must cope with rejection by the family member nearest them, as they face death alone.

Financial problems of adult cancer patients are enhanced because of the uncertainties of the disease. Hospitalization is expensive. The job from which the family draws sustenance may be lost while the breadwinner is ill. Even when it is the housewife and not the man who is ill, financial problems rear their head, because the children must be cared for, and the hospital bills paid.

These financial problems and temporary absences fall into the background when compared with the reality of permanent separation through death, which always lurks in the stage-wings of this human drama. The focus of anxiety, then, usually centers around the care of the children, adequate insurance for their future welfare, and the desire to shield the marriage partner as much as possible from the devastating experience of approaching death.

One mother spent the last three months of her life preparing her 2 adopted children for her death and the onward flow of their lives with a new mother. She said:

"They have had such a hard time of it anyway. They had to go through the trauma of a wartime marriage that broke up and left the two of them drifting. When my husband and I adopted them, we thought all that was behind them forever. Then I got sick. My boy heard from someone that I was going to die and came in with tears streaming and pushed right into the bathroom. I got up and got in there and put my arms around him, and it all came tumbling out. Of course, it was hard, but I talked with him about death and how it was something we all did, and tried to make him feel that when it happened, I would just be waiting with God until he came, like when he went away to camp and then I was there when he came back."

"I had hoped the little girl would be spared, she is just five and it is so difficult for one that age, who knows so much and yet so little, to understand death. One day, I noticed she was sitting in the rocking chair by my bed, digging her toe into the floor and rocking like mad and I looked at her and the tears were running down her cheeks. I said, 'What's the matter, baby?' and she said 'Sally (her little playmate) said you were going to die, and I don't want you to die, 'cause, I love you so much, and then I wouldn't have a mummy.' And then she broke into sobs. I talked to her for a long time and told her that after Mummy was gone away for a while, I wanted Daddy to get her a new mummy to take care of her and Brother and Daddy. She thought for a long time, then she said, 'Well, all right, Mummy, but I won't love that other Mummy like I do you.' "

And so, this gallant mother prepared her children to face death, not as a frightening, incomprehensible blow, but as a natural thing to be met by all, and a door through which the final reunion with those we have loved is accomplished. At the same time, she was preparing them to pick up the broken strands of life and to go forward.

Another mother who had felt she was not responding to treatment prescribed by the physicians was observed trudging down the hospital corridor late one afternoon. The psychologist approached her, because judging from the gait of the patient, her mental attitude was obvious. The patient told the psychologist:

"I have just heard my doom. (Long pause.) I just told the doctor that I realized I was not responding to treatment, and if I had only a short time to live I needed to know. You see,

I have two little girls. My own family is all dead. My husband left me years ago and I don't even know where he is. I have to make some arrangements for someone to take care of my girls. I can't just die and not know what is happening to them. I know a wonderful family that I think might take them for adoption. I've got to do something about them. When I told the doctor this, he told me I had maybe six weeks, maybe three months left. Now, I've got to absorb the shock and get out of here to see about my children."

At this point the patient broke down. She did go home and arrange for the adoption of her children. Then she returned to the hospital, and died within the six-week period.

The patient may often became the emotional Rock of Gibraltar upon whom the family leans, rather than the reverse. The father of 5 children, for instance, continued to guide the destiny of his family from his sickbed for three weary years before his demise. In the meantime, he had instructed his wife and the older children as to the working operations of the small farm from which they wrested their livelihood.

Several couples reported that the terminal years of a patient's life had been the happiest of their time together because they had faced the fact that the marriage partner was going to die, and instead of wasting precious time in useless grief had attempted to make each day as rich and rewarding as possible. One woman said:

"During that last year my husband and I were closer and happier than we had ever been. We were thankful we had this time to say all the things we had failed to say in our crowded lives before, and to do some of the things we had always wanted to do together."

A man whose wife was nearing death said:

"I can only be thankful that we had the last six months together and that we both knew what was going to happen. She was fairly well, and we just air-conditioned the car and went to see all the places she had always talked about and we just felt we couldn't see, or kept saying 'next year.' Now, she is almost gone, but I keep remembering how happy she was and how grateful we were that we could have these rewarding months together."

On occasion, cancer patients must cope with the trauma of a rejecting family member. Husbands have been known to reject their wives because of radical surgery and the ravages of terminal illness. Wives have also rejected husbands when terminal stages incapacitated them. One lovely young mother of 4 small children kept explaining the neglect and rejection by her husband (she had been hospitalized for emotional instability prior to her illness but had been home for several years) and her mother (who was a confirmed alcoholic), while she died alone.

Summary of Anxieties Related to the Family

For the adult cancer patient, anxieties related to the family may be deeply traumatic. Not only must cancer patients bear the brunt of financial outgo for which they are often not prepared, but also debilitating heartbreak as they realize that the temporary separation due to hospitalization may become permanent through death. This stress is great when the family is protective and

loving, but becomes almost unbearable when the patient is rejected and left to face death unsupported and unloved.

SUMMARY

In any severe illness, the need for a humanistic physician who assesses the actual life situation and special psychologic make-up of his patient is great. When the disease is cancer and the patient an adult suddenly shorn of his independent and protective role in the family, this need is intensified. As Sutherland[1] has said, speaking of the cancer patient: "A good patient-physician relationship, beginning with the initial diagnostic examination, is the patient's best guarantee against the development of crippling beliefs and their expression in unnecessary restriction of activities."

The present study concerns the emotional problems revealed by 40 patients as they faced the diagnosis of cancer, the radical treatment involved, and the reality of either returning to active life or meeting imminent death. These problems resolved themselves into 3 major categories of emotional stresses experienced either singly or simultaneously: 1) anxieties associated with the meaning of cancer to the individual, 2) conflicts arising from the precipitation of a productive adult into an unaccustomed and barren hospital world, and 3) emotional components of separation from the family, either temporarily by hospitalization or permanently by death.

This investigation of emotional stresses experienced by adult cancer patients emphasizes the importance of the psychologic role of the doctor. A warm, protective relationship between doctor and patient minimizes many of the emotional problems, and therapeutic management is expedited when the doctor is aware of possible sources of anxiety impinging upon his patient.

[1] Sutherland, A. M.: Psychologic barriers to rehabilitation of cancer patients, *Postgrad. Med.* **7:** 523 (June) 1955.

Abstracts of Current Literature

I^{131}-INDUCED HYPOTHYROIDISM IN INTRACTABLE ANGINA PECTORIS.

Albright, E. C.; Soder, P. D., and Crumpton, C. W. *Ann. Int. Med.* **49:** 271 (Aug.) 1958.

Radioactive iodine therapy should be limited to patients with severe angina who have failed to respond to conventional medical therapy, in whom spontaneous remission is unlikely, whose symptoms are relatively stable, and who are likely to live long enough for the development of hypothyroidism. Twenty-four patients of average age 54.7 years were followed for periods up to fifty-two months. The quantity of I^{131} calculated to induce hypothyroidism was given in a single dose, and subsequent treatment was at three-month intervals as necessary. The dosage was estimated by dividing the thyroidal uptake of a test dose into the product of the estimated weight of the gland times the desired tissue concentration of I^{131} per gram. The dose varied, in all but 1 patient, between 12 mc. and 57 mc.; 1 patient received a total of 106 mc. in three doses. Improvement was judged in accordance with the diminution in number of attacks of pain and in the requirement for nitroglycerine. In 62.5 per cent of the patients there was excellent improvement over the pretreatment status; in 33 per cent, worthwhile improvement; and 1 patient, no change. The degree of symptomatic improvement in general paralleled the degree of hypothyroidism induced, but striking exceptions can occur. No serious side-effects were observed. The symptoms of hypothyroidism in some patients were so severe as to require the administration of thyroid. Occasionally the coronary reserve was so limited that this therapy was attended by the recurrence of angina. Induced hypothyroidism is palliative treatment. Angina will recur as coronary atherosclerosis progresses. Radioactive iodine-induced hypothyroidism is concluded to afford safe and effective therapy in selected patients with severe angina pectoris.

BARBITURATE INTENSIFICATION OF ANTI-ANGINAL ACTIVITY OF NITRITES.

Ant, M. *Am. Pract. & Digest Treat.* **9:** 1387 (Sept.) 1958.

Pentaerythritol tetranitrate alone may provide inadequate relief of severe anginal pain. When the effects of this drug alone, of placebo, and of a combination of pentaerythritol tetranitrate with amobarbital in timed-disintegration form were compared, a superior degree of pain relief was obtained with the combination—about 97 per cent of patients so treated experienced substantial reduction in anginal pain. Another indication of improvement was reduction in shortness of breath, which was most marked with combined therapy. Patients who improved experienced increased ability to walk, an increase in the sense of well-being, and a decrease in fear of repeated anginal attacks. The 30 patients with angina were of average age 54.7 years. The anginal syndrome had been present for an average of three years. The most effective combination contained 30 mg. each of pentaerythritol tetranitrate and of amobarbital per sustained-release capsule, and was given twice daily. The better result obtained with the combined therapy was attributed to enhancement by the barbiturate of the action of pentaerythritol tetranitrate, which could be used in smaller doses. No side-effects occurred because of the low effective dose of pentaerythritol tetranitrate in the combination and the use of capsules constructed on the timed-disintegration principle. This combination is the agent of choice for the treatment of anginal pain in older people who are likely to have extensive atherosclerosis. A double dose of the combination has been found more effective when hypertension is also present.

OCCULT INTESTINAL BLEEDING AS A CAUSE OF ANEMIA IN ELDERLY PEOPLE.

Bedford, P. D., and Wollner, L. *Lancet* **1:** 1144 (May 31) 1958.

The concept of a physiologic anemia in old age is erroneous. A study in 156 unselected patients aged 65 or more, with no overt hemorrhage, showed 41 per cent of them to be

anemic with hemoglobin levels below 80 per cent (11.7 Gm. per 100 ml.). The anemia in the majority was of the iron-deficiency type. In twice as many anemia patients as non-anemia patients there was a positive reaction for occult blood in the stools. This highly significant statistical difference is interpreted to indicate a direct causal relationship between anemia and occult intestinal hemorrhage in the elderly patients studied. This definition of anemia is defended and the validity of the Gregersen test for occult blood substantiated. It is pointed out that anemia in the elderly may be manifested only intermittently, so that serial determinations of hemoglobin are necessary to detect it. A careful inquiry as to the cause of anemia in elderly persons should be made, and especially an investigation as to the source of any blood loss. Sixty-four per cent of the anemia patients in this study had organic lesions but in 34 per cent no cause could be found.

STOKES-ADAMS DISEASE IN OLD AGE.

Biss, K., and Lev, M. 31st Scientific Session, Am. Heart Assoc., *Circulation* **18:** 695 (Oct.) 1958, Part 2.

Four cases of Stokes-Adams disease in people over the age of 60 were studied. They all presented an identical clinical and pathologic picture. There was no history, or evidence on physical examination, of congenital cardiac defects, valvular disease, myocarditis, or coronary artery disease. The presenting symptoms were syncope or convulsions. The electrocardiograms showed varying degrees of A-V blocks, and during the attacks ventricular tachycardia or fibrillation was observed. At necropsy all 4 patients showed only minimal narrowing of the coronary arteries and no myocardial infarction. The outstanding feature was a marked thickening in the region of the base of the aortic leaflet of the mitral valve, extending into the membranous portion of the interventricular septum. In 1 patient there was calcification within the lesion. Detailed histologic studies of the conduction system were made in 1 patient. This revealed fibrosis and calcification at the summit of the ventricular septum, with scar formation at the junction of the bundle of His and the right and left bundle branches. The conduction system of a second patient is being studied. A review of the literature reveals that this type of Stokes-Adams disease was last comprehensively studied by Yater in 1935 but has been neglected in recent years. This paper re-emphasizes the frequency and the importance of this type of Stokes-Adams disease seen in patients beyond the age of 50 years.

RADIOGRAPHIC DIAGNOSIS OF ATHEROSCLEROSIS.

Brogdon, B. G., and Crow, N. E. *U. S. Armed Forces M. J.* **9:** 1274 (Sept.) 1958.

The radiographic demonstration of atherosclerotic vascular calcification is always significant. As an indication of serious generalized disease, it is a sign that should be carefully sought in every roentgenologic examination. Its detection by radiography provides an excellent opportunity to study and treat subclinically affected individuals prior to the evaluation of severe complications. In patients with clinical manifestations, the finding of atherosclerotic calcification may supply important diagnostic clues. (From authors' summary.)

STUDIES ON DEXAMETHASONE, A NEW SYNTHETIC STEROID, IN RHEUMATOID ARTHRITIS—A PRELIMINARY REPORT. ADRENAL CORTICAL, METABOLIC AND EARLY CLINICAL EFFECTS.

Bunim, J. J.; Black, R. L.; Lutwak, L.; Peterson, R. E., and Whedon, G. D. *Arthritis & Rheumatism* **1:** 313 (Aug.) 1958.

Physiologic, metabolic, and early clinical effects of dexamethasone, a new synthetic corticosteroid, have been described. On a weight basis (mg. for mg.) the capacity of dexamethasone to suppress the corticotropin secretion of the adenohypophysis in man is about thirty times greater than that of prednisone and its antirheumatic potency approximately six times that of prednisone. In both types of biologic activity, dexamethasone is the most

potent steroid thus far synthesized; yet it does not inhibit adrenocortical elaboration of aldosterone or impair aldosterone responsiveness to sodium loss or deprivation. In dosages which are adequate to suppress symptoms of disease activity in rheumatoid arthritis, that is, fractions of 1 mg. to 4 mg. daily, or even in larger experimental dosages (10 mg. daily), there is no retention of sodium or loss of potassium. In dosages of 6 to 10 mg. daily, increased excretion of nitrogen and appreciably negative calcium and phosphorus balances are produced. Carbohydrate tolerance is unimpaired when dexamethasone is given to patients with rheumatoid arthritis in therapeutic dosages for as long as ten weeks. Dexamethasone was subjected to clinical trial for periods up to twelve weeks in 18 patients with rheumatoid arthritis whose disease had not adequately been controlled by therapeutic measures in current use. In 16 patients with active rheumatoid arthritis, administration of dexamethasone in dosages varying from 0.8 to 4.0 mg. daily was followed by marked subjective and objective improvement in 5, moderate improvement in 7, and slight improvement in 4. In 2 additional cases of unusual severity, a daily dosage of 6.0 mg was explored briefly with unsatisfactory results. In 3 of the cases that responded satisfactorily, aspirin was added to dexamethasone therapy in order to reduce the need for higher steroid dosage. Minor undesirable side-effects were noted in 14 of the 18 patients studied. No major toxic effects occurred during the brief period of trial. (From authors' summary.)

A REVERSIBLE NEPHROTIC SYNDROME ASSOCIATED WITH CONGESTIVE HEART FAILURE.

Burack, W. R.; Pryce, J., and Goodwin, J. F. *Circulation* **28:** 562 (Oct.) 1958.

Case reports are presented of 4 patients in whom the nephrotic syndrome occurred during the course of chronic heart failure. In each case, gross proteinuria, massive edema, hypoalbuminemia, abnormal plasma electrophoretic patterns and hypercholesteremia developed, with a normal or slightly elevated blood urea level and a normal urinary sediment. Three patients recovered in a period of nine months during a regimen of digitalis, low-salt high-protein diet, and the regular weekly intramuscular injections of a mercurial diuretic. Intravenous aminophylline given prior to the diuretic enhanced its effect. No renal or other disease could be found in these patients to account for the nephrotic syndrome. The cause is not mercurial toxicity but probably something related to heart failure per se. The possible relation of the proteinuria commonly found in heart failure (the cause of which is unknown) to the occasional occurrence of the nephrotic syndrome is discussed. There is no contraindication to continuing mercurial diuretics when the nephrotic syndrome develops during heart failure, provided no evidence of toxicity, such as a rash or abdominal pain, is apparent. The administration of these diuretics does not prevent the reversibility of the nephrotic syndrome.

EFFECT OF RELAXIN ON OCCLUSIVE PERIPHERAL ARTERIOSCLEROTIC DISEASE.

Casten, G. G., and Gilmore, H. R., III. 31st Scientific Session, Am. Heart Assoc., *Circulation* **18:** 702 (Oct.) 1958, Part 2.

The beneficial effect on Raynaud's phenomena and ischemic ulceration in scleroderma exerted by relaxin prompted a study of its effect on 8 patients with arteriosclerosis obliterans. Prior to relaxin therapy, the mean of 3 determinations of skin temperature under conditions of maximal vasodilation in 36 abnormal toes was 27.3°C. Continuous relaxin therapy (7.5 mg. to 20 mg. intramuscularly daily) was then begun, coupled with estrogen "priming" (Premarin, 1.25 mg. three times weekly). Skin temperature measurements, at intervals of two weeks to one month, revealed a progressive rise. After three months of therapy, the mean level had increased to 30.9°C. Every toe studied showed an increase. After four months of therapy, all toes had reached a normal range of 30.0°C. or above. Patients studied after six months of continuous therapy maintained a normal range. Dis-

continuation of therapy was followed by return to pretreatment values. Studies of blood flow to the calf muscles employing direct stimulation ergometry (Edwards-Murphy Ergometer) were made in 3 patients. A twofold increase or more in ergometric "energy units" occurred after three months of therapy. A further increase (four times the control value) occurred after five months of therapy in 1 patient. This increase coincided with subjective improvement in all patients. Relaxin exerts a known effect upon connective tissue and presumably alters collagen. Although the manner in which relaxin produces a striking increase in blood flow to the extremity is unknown, this hormone offers promise in the therapy of obliterative vascular disease.

APPENDICITIS IN THE AGED.

Christensen, E. *Brit. M. J.* **2:** 832 (Oct. 4) 1958.

Appendicitis is not rare in elderly people. Among 1,254 cases of acute appendicitis in a surgical department, 7 per cent occurred in patients aged 60 years or more. The mortality rate among them was 5.6 per cent compared with a rate of 0.34 per cent among younger persons. The incidence of complications (perforation alone or with abscess, peritonitis) was four times as great in the older group. The absence of alarming symptoms in elderly people may lead to early gangrene and perforation. These signs may be absent because the peritoneum of the aged reacts only slightly, and muscular guarding is seldom found because of the relaxed abdominal wall. Blunting of the sense of pain and weakening of the bowel reflexes leads to less nausea and vomiting, and constipation may mask any symptoms that may be present. Widespread arteriosclerosis leads to vascular occlusion and the early onset of ischemic gangrene and perforation. More than three times as many postoperative complications occurred in the patients in this series who were over age 60 as in the younger patients. Early operation is advised even in elderly persons unless a palpable lump is present. Such cases were treated conservatively with opium and antibiotics and appendectomy performed after four to five months. Early operation permits the detection of cecal and appendiceal tumors. It is recommended that the right colon be examined when elderly patients undergo an operation for acute appendicitis.

THE ELECTROCARDIOGRAPHIC FINDINGS IN SMALL, ATYPICAL MYOCARDIAL INFARCTS.

Clagett, E. H., Jr. *Circulation* **28:** 548 (Oct.) 1958.

In a study of 359 patients with myocardial infarction, the electrocardiograms were divided into those with significant Q waves (typical) and those with normal QRS complexes (atypical), and the clinical data were correlated with these findings. Thirty-one patients showed changes in the precordial leads; 14 showed changes in leads II, III, and aV_F. Seven patients showed significant ST segment elevation. In only 4 patients with atypical infarction did a delay occur in the development of electrocardiographic abnormalities; the interval was five days in 2 patients, one week in 1 patient, and two weeks in 1 patient. The mortality rate among the atypical cases was 2.3 per cent (1 elderly, obese diabetic woman died; infarction in this case would not have been called atypical or mild on clinical evaluation) compared with 27.3 per cent in the typical cases. The only complication in the atypical cases was a bout of transient atrial fibrillation (incidence 2.3 per cent). The incidence of complications among the typical cases was 32 per cent. A study of 33 patients who could be followed for five to ten years following an atypical infarction showed the prognosis to be more favorable than that following typical infarctions. Approximately one-third remained healthy. A subsequent typical infarction occurred in 3 patients and 4 suffer from angina. Six patients died from cardiac disease and 8 others from other causes. It is concluded that the immediate prognosis in atypical myocardial infarction is excellent and that the electrocardiogram can be of assistance in making the diagnosis.

ARTERIAL RIGIDITY IN HYPERTENSION.

Conway, J.; Busby, E., and Hoobler, S. W. 31st Scientific Session, Am. Heart Assoc., *Circulation* **18:** 706 (Oct.) 1958, Part 2.

In view of the importance of arterial degenerative vascular diseases in hypertension, an attempt has been made to develop a clinical test by which it may be possible to detect changes in the elastic properties of the great vessels. The test showing most promise depends upon changes in pulse pressure which occur as the diastolic pressure is suddenly reduced by inhalation of amyl nitrite. Since publication of the details of the method, an unselected group of 70 hypertensive patients has been investigated. The results show that most patients with renal hypertension have normally elastic arteries, whereas those with essential hypertension usually have increased rigidity of the large arteries. Patients with rigid arteries have, as would be expected, high systolic pressure and moderate elevation of diastolic pressure. The cardiac output, determined by the dye method, is in the normal range but the total peripheral resistance is increased (range 1370–2270 dynes/cm.$^{-3}$). It is of interest to find that rigidity of the arterial tree is associated with other evidence of arterial degeneration—unfolding of the aorta, cerebrovascular and coronary disease. The incidence of these complications is twice as high in hypertensive patients with rigid arteries as in those with normally elastic vessels. It has also been found that a positive family history of cardiovascular disease is more frequent in patients with rigid arteries and there is a greater fall in blood pressure in response to bed rest and to test doses of ganglion blocking agents.

OVARIAN ESTROGENIC TUMORS AND DIFFUSE ESTROGENIC THECOMATOSIS IN POSTMENOPAUSAL COLPORRHAGIA. THE IMPORTANCE OF THE BENIGN ENDOMETRIAL MITOSIS.

Fienberg, R. *Am. J. Obst. & Gynec.* **76:** 851 (Oct.) 1958.

Women with colporrhagia after more than three years of postmenopausal amenorrhea and with a benign hyperplastic endometrium containing mitotic figures, with or without a palpable pelvic tumor, are likely to have a thecoma, a mixed granulosa-cell and theca-cell tumor, or estrogenic thecomatosis. Provided no estrogen has been administered, such a woman should undergo an exploratory laparotomy. This recommendation is based upon an analysis of 5 cases of estrogen-secreting ovarian tumors and 1 case of diffuse ovarian thecomatosis found upon review of the records of 140 cases of postmenopausal hemorrhage in women over 60 years of age who had undergone curettage. The presence of active estrogen secretion was indicated by finding benign endometrial mitoses with hyperplasia. The importance of this finding as an indicator of estrogenic activity is stressed. Attention is also drawn to 2 of the cases in which postmenopausal colporrhagia ceased after curettage despite the presence of an estrogen-secreting ovarian tumor. This refutes the previous assumption that an estrogenic ovarian tumor is absent in such cases.

NEW ANTIHYPERTENSIVE DRUG, 1-PHENYL-2-HYDRAZINOPROPANE.

Gillespie, L., Jr.; Terry, L. L., and Sjoerdsma, A. 31st Scientific Session, Am. Heart Assoc., *Circulation* **18:** 724 (Oct.) 1958, Part 2.

Recent studies have been designed to correlate changes in the metabolism of vasoactive monoamines such as serotonin and norepinephrine with alterations in blood pressure. It was found that a monoamine oxidase inhibitor, 1-phenyl-2-hydrazinopropane, markedly lowered the blood pressure in severe hypertension. The drug was administered to a small group of hospitalized patients with hypertension in single oral doses of 12.5 to 50 mg. daily for twelve to twenty-five days. Significant lowering of the blood pressure was noted in each case, the predominant effect being on the standing pressure. The range of maximal decreases in standing pressure was 57–108/44–68 mm. Hg. Maximal effects were apparent

within the first ten days of therapy, and the standing pressures returned to control levels seven to fourteen days after stopping therapy. A larger group of outpatients were maintained on 6.25 to 25 mg. of the drug per day for at least two months. Satisfactory control of blood pressure was achieved in every case, using this agent alone or in combination with chlorothiazide. Although this drug effectively inhibits monoamine oxidase in man, it has not been proved that this action accounts for the hypotensive effects. The absence of undesirable side-effects warrants further trials of this agent in the management of hypertension.

THE MANAGEMENT OF CORONARY DISEASES AND ANGINAL SEIZURES.
Goldberg, L. H. *J. Michigan M. Soc.* **57:** 969 (July) 1958.

An extract containing the total alkaloids of the plant *Chelidonium majus* and known as Kelid relieved anginal pain in 42 patients grouped as follows: postmyocardial infarction, 11; coronary artery disease with abnormal electrocardiogram at rest, 18; coronary artery disease with normal electrocardiogram at rest, 9; hypertensive cardiovascular disease with abnormal electrocardiogram at rest, 3; and hypertensive cardiovascular disease with normal electrocardiogram at rest, 1. Symptomatic relief was obtained in all patients and improvement in the electrocardiogram in a few patients in which it was abnormal. Improvement usually occurred within two weeks, and the patients usually were symptom-free within two months and able to resume reasonable amounts of physical activity. Thereafter, in the majority, the drug could be discontinued without the recurrence of attacks. No toxic effects were observed; side-effects such as nausea were minor and rare. The recommended dosage of Kelid is 0.25 cc. orally three times daily. The drug is not incompatible with digitalis, antispasmodics, quinidine, or nitroglycerine. Kelid appears to act by increasing coronary blood flow during the diastolic phase of the cardiac cycle. It does not affect blood pressure nor have an antispasmodic effect.

WHITE LESIONS OF THE VULVA.
Hyman, A. B., and Falk, H. C. *Obst. & Gynec.* **12:** 407 (Oct.) 1958.

It is pointed out that the vulva includes both skin and mucocutaneous tissue—a distinction not always made. *Lichenification* of the vulva is that condition in which the *skin* of the vulva becomes thickened and somewhat hyperkeratotic, with increase in skin markings so as to form plaques composed of closely set, usually flat-topped papules. Intense pruritus is associated with it. Scratching probably causes a "protective" thickening of the skin in patients with a predisposition to this type of reaction. The disease may spread to the mucocutaneous areas and there simulate leukoplakia. Lichenification is not a precancerous lesion. Its histologic characteristics, and those of the other conditions considered, are outlined. Corticosteroid, tar, Vioform, zinc oxide ointment, ichthyol paste, or Calmitol may be applied locally. Repeated radiation with roentgen rays is not recommended; grenz rays and thorium-X provide safer therapy. *Leukoplakia* affects mucosal and/or mucocutaneous tissues in which thick white plaques develop. It is limited primarily to older age groups. Lichenification of adjacent skin is a commonly associated finding. Both of these may complicate other diseases of the vulva. A good history and clear indication of the biopsy site make it possible to distinguish microscopically between leukoplakia and lichenification. It is not rare for a malignant condition to develop in a leukoplakic lesion, but carcinoma of the vulva can develop in the absence of this disease. Erosions, ulcers, or keratoses in leukoplakia warn of the possibility of malignancy. Antipruritic therapy for leukoplakia is the same as that for lichen chronicus simplex. If diabetes is present, it must be controlled concomitantly. *Bowen's disease* resembles an exaggerated leukoplakia and may involve both skin and mucocutaneous tissue. It affects adults, particularly those in older age groups. It can be recognized by the rough, verrucous, hyperkeratotic lesions found in most cases. Histologically, the most important feature is the great variety of cell and nucleus types found in the epidermis. This is a pre-

cancerous condition, the treatment for which is vulvectomy. Various atrophic states have been referred to as kraurosis vulvae, but the majority of cases show thinning of the skin often associated with fragility of tissues, so that they actually represent *lichen sclerosus et atrophicus*. It is considered untenable to distinguish between kraurosis vulvae and lichen sclerosus et atrophicus on the basis of changes in the vessels of the deep cutis. The latter disease involves both skin and mucocutaneous tissue. The "cigarette-paper" wrinkling of the surface of affected sites is characteristic. Although the vulva is usually white with fine telangiectasis, the area in early stages may be bright red. Itching is a common symptom. Leukoplakia and lichenification may be associated with it. Malignancy reported in this disease has most likely developed in associated leukoplakia. Lichen sclerosus et atrophicus responds symptomatically to antipruritic agents. Chloroquine, 250 mg. two or three times daily for one month, may be tried. Only instances of essential tightening of the introitus such as are associated with senility should be referred to as *kraurosis vulvae*. There may be atrophy of the epidermis and looseness of the connective tissue. Kraurosis vulvae may be helped by dilators. Estrogens have not proved to be of value. Histologically, the lower layers of the epidermis in *Paget's disease* contain cells or groups of cells that are swollen, have lost their intercellular bridges, and become rounded. The cytoplasm is light-staining; the nucleus is reticulated. The skin submitted for biopsy may show carcinoma of the apocrine glands in the cutis beneath the affected epidermis. The treatment is vulvectomy.

DIE ALKALISCHE PHOSPHATASEAKTIVITÄT DER BLUTZELLEN BEI LEUKOSEN UND ANDEREN PATHOLOGISCHEN ZUSTÄNDEN. (THE ALKALINE PHOSPHATASE ACTIVITY OF THE BLOOD CELLS IN LEUKOSES AND OTHER PATHOLOGIC STATES).

Lambers, K. *Ztschr. klin. Med.* **155:** 176, 1958; through Ciba Literature Review **3:** 244, 1958.

The determination of alkaline phosphatase in blood specimens has acquired importance in the management of hemopathies, particularly with respect to the differential diagnosis. It has been found, for example, that the alkaline phosphatase activity of the granulocytes is greatly reduced in chronic myelosis. This finding hardly changes in the course of cytostatic therapy or during remission. When acute leukosis is present, however, the proportion of phosphatase-positive granulocytes may be normal or even elevated; in advanced cases, it is reduced as a rule, but successful treatment produces a rise to normal or excessively high values. These findings suggest that there is a fundamental difference between the 2 diseases: chronic myelosis involves the entire granulopoietic system, but in acute leukosis the disease primarily affects the myeloblasts. In the case of inflammatory reactions, which are often difficult to distinguish clinically from chronic myelosis, the phosphatase-positive granulocytes are increased. The same is true of osteomyelosclerosis. The percentage of phosphatase-positive granulocytes is lower in the bone marrow than in the peripheral blood. Maturation influences must account for this observation.

OBSERVATIONS ON AMANOZINE (W-1191-2), A TRIAZINE DIURETIC COMPOUND.

Miller, D. V., and Ford, R. V. *Am. J. M. Sc.* **236:** 32 (July) 1958.

Amanozine, a nonmercurial diuretic and an analog of chlorazanil, chemically is 2-amino-4-anilino-1,3,5-triazine hydrochloride. Investigation of the effectiveness of this compound showed the daily dose to be between 150 and 300 mg. No additional increase in sodium or water excretion could be secured with a dosage of 600 mg. daily. The onset of action occurred within two hours following oral administration. The effect of the drug persisted for twelve to eighteen hours. Amanozine behaves as a potent "water diuretic," but it has only a slight effect upon sodium excretion. The drug augments the orthostatic hypotensive effect of Rauwolfia and ganglion-blocking agents when used in combination with them. Reversible depression of renal hemodynamics and retention of nitrogen and phosphate occur upon chronic administration. Therefore, the use of amanozine demands

caution and should probably be limited to a short-term or interrupted schedule. The electrolyte excretion pattern following amanozine shows its mechanism of action: increased excretion of water associated with increased excretion of sodium, chloride and bicarbonate. The excretion of ammonia and the titrable acidity of the urine are depressed in reverse relationship to these. This pattern simulates that following administration of chlorazanil. Both compounds differ in their mechanism of action from mercurials, carbonic anhydrase inhibitors, and chlorothiazide, which suggests still another mode of diuretic behavior.

ENTWICKLUNG VON KANKROIDEN BEI BRILLENTRÄGERN (DISCOVERY OF CANCROIDS IN SPECTACLE WEARERS).

Otto, J. *Klin. Monatsbl. Augenheilk.* **132:** 504, 1958; through Ciba Literature Review **3:** 229, 1958.

In one year, 4 patients were seen who had worn spectacles for many years, and in whom cancroids had developed at various places where the frames rested. To establish a causal connection between the trauma and the development of a tumor, 5 prerequisites must be fulfilled: 1) There must be unmistakable evidence of trauma and of a primary tissue lesion —in this group, epithelial lesions caused by the wearing of spectacles and followed by regenerative processes. 2) The trauma and its sequelae must have the same location—confirmed in the present patients by the fact that the tumors occurred only where there was constant pressure from spectacles (flap of the ear, root of the nose). 3) There must be evidence of regeneration processes of long standing. In this series, months before the actual appearance of the tumor, minor changes could be detected in the skin at the same place, and only after some time did the tumor suddenly proliferate and become enlarged. 4) There must be a latency period. In practice, this means the length of time spectacles have been worn. This period was five to twenty-three years among this group of patients. 5) Predisposition to tumor must be taken into account. This is difficult to demonstrate in practice, and could be confirmed in only 1 of these cases. This patient had had a basal-cell carcinoma at the corner of the left eyelid and wore spectacles for cosmetic reasons. Within five years, a cancroid developed on the pinna of the left ear at the place where the curved portion of the spectacle frame rested.

ORAL SUSTAINED-RELEASE NITROGLYCERINE TABLETS IN ANGINA PECTORIS.

Plotz, M. *Am. Pract. & Digest Treat.* **9:** 903 (June) 1958.

Nitromed-CR contains nitroglycerine adsorbed on minute "sugar" granules which are coated in such a manner in a compressed tablet as to disintegrate at different times and release the drug in the gut at a uniform rate over a period of eight to ten hours. Tested in 197 patients, aged 39 to 81 years, with organic heart disease and unequivocal angina pectoris relieved by nitroglycerine, this sustained-release preparation of nitroglycerine in a dosage of $\frac{1}{25}$ gr. twice daily permitted a markedly reduced dosage of sublingual nitroglycerine tablets in 180 patients. Some could dispense with the "regular" tablets. Seventeen patients failed to benefit. Approximately the same percentages of patients were benefited in each of 3 groups of patients who had formerly required 20 or more, 10 to 19, or 4 to 9 nitroglycerine tablets per day, respectively. Side-actions accompanying the use of this preparation were slight giddiness or dizziness in 36 patients. Not only does the drug in this form have value for prophylactic use but it is obviously convenient for the patient.

ADRENO-LIENALER SHUNT BEIM METASTASIERENDEN MAMMAKARZINOM (ADRENOLIENAL SHUNT IN METASTATIC BREAST CANCER).

Walser, A.; Hess, W.; Meier, A. L., and Spring, P. *Deutsche med. Wchnschr.* **83:** 580, 1958; through Ciba Literature Review **3:** 232, 1958.

An adreno-lienal shunt operation was performed as a palliative measure on 6 patients with metastatic breast cancer. The rationale for this operation was as follows: Elimination of endogenous estrogens produces improvement in many cases of breast cancer. Castration

alone does not deprive the body of all of its estrogen because the hormones secreted by the adrenal cortex can be converted into estrogens. Total adrenalectomy, on the other hand, entails substitution therapy for the remainder of the patient's life. The adreno-lienal shunt operation was developed in order to spare patients this substitution therapy and yet to render estrogens ineffective. By means of the shunt, the venous adrenal blood is diverted from the greater circulation and conveyed to the splenic vein, that is, to the portal circulation. The sex hormones are then broken down in the liver. Two to three weeks before the adreno-lienal shunt operation, the patients were subjected to right-sided adrenalectomy and bilateral oophorectomy. In all 6 cases, subjective improvement occurred, and 1 had a good objective remission. Substitution therapy was unnecessary in 5 patients. In 1 case, however, thrombosis of the shunt and thus adrenocortical insufficiency developed following the operation. The picture here resembled that of total adrenalectomy and rendered cortisone substitution necessary.

SURGICAL LESIONS OF THE LOWER EXTREMITIES IN DIABETES. A CLASSIFICATION OF LESIONS ARRIVED AT CLINICALLY, APPLICABLE AS A GUIDE TO SURGICAL PROCEDURE.

Williams, F. W., and O'Kane, T. J. *J. Michigan M. Soc.* **57:** 976 (July) 1958

Lesions of the lower extremities in diabetic patients can be classified clinically, as follows: I. Vascular: marked arterial deficiency without evidence of infection; the initial lesion is gangrene. II. Mixed, 3+ vascular, consisting of a vascular lesion with marked arterial insufficiency, initially gangrene, with superimposed infection. III. Mixed, 2+ vascular, characterized by moderate vascular insufficiency; the initial lesion is infection upon which gangrene is superimposed. IV. Mixed, 1+ vascular, with slight arterial insufficiency; the lesion initially is infectious in type but the circulation is adequate to prevent gangrene from being superimposed upon it. V. A purely infectious lesion. The degree of arterial impairment and the severity and extent of infection are determined by examination of the leg. A tabulation is presented of the local and systemic findings in each class of lesion. The most important systemic findings are age, evidence of arteriosclerosis in radial, retinal, and coronary arteries, concomitant disease, and manifestations of infection. The local findings include all of the observations on the leg and foot such as the presence of pain, arterial thickening, diminution of arterial pulsations, vein refilling, and capillary circulation. The classification presented is useful as a guide to management. The principles which apply here are that 1) infection can be controlled by appropriate sulfonamide and antibiotic therapy (conservative management is likely to succeed for legs in which there is little or no impairment of circulation), and 2) any surgical procedure that is indicated must be performed at a level where the circulation is adequate (as determined by careful clinical estimation of the circulatory status of the leg) in order to cope with the trauma of the surgical procedure. Observation of the latter principle should avoid repeated amputations. Superficial Class I lesions can be treated conservatively as long as there is no spread of gangrene and no infection. Should there be extension beyond the toe or into the web space, in the absence of infection a modified guillotine amputation between the ankle and knee may be performed. Lesions that are extensive require amputation above the knee, preferably at the supracondylar level. In mixed lesions, indicated therapy is as follows: Class II lesions; amputation above the knee if antibiotic or chemotherapy has not controlled spreading infection or gangrene. Class III; with successful control of infection, a modified guillotine technic frequently may be employed below the knee or at the mid-calf. Class IV; (a) superficial lesions require only antibiotic therapy; (b) when the lesion is localized, incision and drainage or amputation of a toe may be attempted, provided there is no gangrene; (c) if infection is spreading despite appropriate therapy, modified guillotine amputation of the lower leg is indicated. Superficial infectious lesions are treated conservatively; when they are localized, incision and drainage with intensive sulfonamide and antibiotic therapy are indicated. The only amputation used in these cases is that of a toe in order to "pie-cut" a foot and drain the infection adequately.